THE USE OF AN ANTIOXIDANT GEL IN MODIFYING THE SIGNS AND SYMPTOMS OF ORAL LICHEN PLANUS

A Thesis

By

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ABSTRACT

The purpose of this study was to evaluate the treatment effect of an antioxidant gel on modifying the signs and symptoms of oral lichen planus. The gel contains the antioxidants phloretin and ferulic acid, as well as the essential oils menthol and thymol.

Twenty-eight patients with oral lichen planus from the Texas A&M University College of Dentistry Stomatology Center and from Dr. Plemons' private practice in Dallas, TX qualified and consented to be in the study. Participants were randomly assigned to a treatment or a placebo-control group. Each patient was evaluated at three visits (baseline, 4 weeks, and 8 weeks). At each visit, electronic surveys were taken to determine participants' discomfort (measured using VAS) and the oral health impact of their disease (measured on a modified version of Oral Health Impact Profile-14). In addition, intraoral photographs were taken at each visit to monitor clinical severity of the disease (measured using a Reticular-Erythematous-Ulcerative scoring system). Patients were instructed to apply the assigned gel three times daily, after brushing their teeth.

The treatment group showed statistically significant differences ($p < 0.05$) in discomfort between baseline (41.25 ± 25.16) and 4 weeks (27.50 ± 23.76) and between baseline and 8 weeks (18.92 ± 7.96). The control group showed no significant changes in discomfort. There were no significant differences between groups in improvement of oral health impact from baseline to 4 weeks. At 8 weeks, there was a significant difference ($p < 0.05$) in the reported improvement in the categories of "trouble pronouncing words" and "painful aching" in the treatment group compared to the control group. The treatment group did not show a statistically significant difference ($p < 0.05$) in clinical severity between baseline (13.00 ± 13.99) and 4 weeks ($9.46 \pm$

5.68), but this difference became statistically significant if a greater p-value was used ($p < 0.10$). There was not a statistically significant difference in clinical severity between baseline and 8 weeks in either group.

Application of a topical antioxidant gel is an effective means of reducing discomfort in patients with oral lichen planus and may also reduce the clinical severity of the disease.

DEDICATION

To Kyle, for unwavering support.

To Mom and Dad, for love and encouragement.

To Ranger, for making me smile.

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Oral Lichen Planus

Background

Lichen planus is a non-infectious mucocutaneous disease that can affect the skin, oral mucosa, genitalia, scalp, and nails. First defined by Wilson and Kaposi in 1866, it is thought to be a chronic T-cell mediated immunological disorder; however, despite extensive research, the etiology is still unknown.[1] Oral lichen planus affects 0.5 to 2.2% of the population and is most often found in middle-aged female adults of all ethnicities.[2] In a report that followed 723 patients in a dermatologic clinic with oral lichen planus over a period of 6 months to 8 years, it was found that 75% of patients with lichen planus were women, with a mean age of 57 years at presentation.[3] Another study that retrospectively examined 690 patients from one group of Oral Medicine specialists in England found that 68.7% of affected patients were Caucasian.[4]

Lichen planus is characterized by pain or discomfort that may interfere with the patient's function and quality of life, as symptoms can vary from minor mucosal sensitivity to continuous debilitating pain. Symptoms can occur for months or years with periods of exacerbation and quiescence. Periods of exacerbation are characterized by increased erythema, ulceration, pain, and sensitivity, whereas in quiescence periods patients exhibit decreased erythema, ulceration, pain, and sensitivity. The clinical form of oral lichen planus may determine the severity of the patient's symptoms.

Clinical Presentations

There are six clinical presentations of oral lichen planus: reticular, atrophic, erosive, papular, plaque, and bullous.[1] The most common form, reticular, is characterized by a white, lacy pattern on the buccal mucosa, referred to as Wickham striae. It is typically asymptomatic[5];

however, the reticular form can progress to other types such as the atrophic and erosive forms, which can cause a loss of epithelial integrity and tend to be more symptomatic, requiring treatment.[2]

Atrophic oral lichen planus mostly affects the attached gingiva[6] and presents as erythema, with a typical desquamative gingivitis appearance at the gingiva.[7] Although desquamative gingivitis is characteristic of the atrophic form of oral lichen planus, it can be found in other forms of oral lichen planus, as well as in other mucocutaneous diseases, such as mucous membrane pemphigoid and pemphigus vulgaris.[8] While pain is the most frequent complaint of these forms, patients also report burning, swelling, and bleeding when brushing their teeth.[9]

Erosive oral lichen planus is often considered the most advanced type.[10] It presents as erythematous erosions and ulcerations of the mucosa and typically has a bi-color appearance, with white hyperkeratotic lesions demarcated from ulcers or erosions with a sharp red line. [11] When this form is present, it is most commonly unilateral, but bilateral presentations can be seen as well. [11] While some experts combine the atrophic and erosive forms into one subtype due to their similar appearances, it is important to note that the two forms are two distinct entities with different clinical appearances and can occur together.

The papular subtype consists of white, pinhead-sized patterns that are slightly elevated anywhere in the mouth.[12] The papular form is often present in the initial stages of lichen planus, but often disappears over the duration of the disease and does not redevelop.[12] As a result, this form is rarely observed clinically,[13] as it disappears before patients present with symptoms.

Plaque-like oral lichen planus presents clinically similar to leukoplakia and is difficult to distinguish between the two without a biopsy. [14] Thorn and others reported that plaque-type lesions were found more frequently among smokers than among nonsmokers, and noted that it is

considered to be a chronic form of oral lichen planus, as it is found with equal frequency at the first examination and the most recent.[12] The final subtype, bullous oral lichen planus, presents as a bulla or vesicle that may easily rupture, leaving an ulcerated appearance to the mucosa which is known to be painful to patients.[15]

The buccal mucosa is the most frequently involved site, followed by the lateral borders of the tongue and gingiva.[9] According to a retrospective study of nearly 700 British patients with oral lichen planus, there was not a significant association between the subtype of oral lichen planus and the site.[4]

Immunologic Aspects and Histology

Although one study has theorized that the etiology of oral lichen planus is an autoimmune response to epithelial antigens,[16] most studies theorize that triggers cause the dysregulation of T cells. These triggers may be local[17] or systemic[18] inducers of cell-mediated hypersensitivity, stress[19], or microorganisms, such as Hepatitis C.[20] The histological appearance of lichen planus is marked by an inflammatory infiltrate of almost entirely T-cells, the majority of which are activated CD8+ T-cells.[21] It has been hypothesized that activated CD8+ lymphocytes may initiate the apoptosis of keratinocytes. When keratinocyte apoptosis occurs normally, it plays an important role in maintaining epithelial thickness[22]; however, when dysfunctional, keratinocyte apoptosis can lead to skin and other mucocutaneous diseases, such as oral lichen planus.

Due the cytotoxic properties of the CD8+ T-cells viewed in oral lichen planus and the fact that the lymphocytes were blocked partially by an anti-MHC class I antibody, it is thought that CD8+ lymphocytes detect the antigen associated with MHC class I located on keratinocytes. After this antigen recognition and activation, keratinocyte apoptosis is activated by the CD8+ lymphocytes.[21] Histologically, basal cell and basement membrane degeneration are often seen in

the erosive form of oral lichen planus; keratinocyte apoptosis, triggered by CD8+ lymphocytes, supports this hypothesis.

The exact mechanism by which cytotoxic T cells kill the basal keratinocytes remains unknown, although most proposed mechanisms would implicate a caspase cascade that results in the apoptosis of keratinocytes. Possible mechanisms include the binding of T-cell-secreted TNF-α to a receptor on the surface of keratinocytes, the binding of T-cell surface CD95L to the surface of keratinocytes, or the entrance of T-cell-secreted granzyme B into the keratinocyte by pores.[23]

Although most of the cells identified in oral lichen planus are CD8+ lymphocytes, CD4+ helper T-cells have also been identified.[24] MHC class II antigens present to CD4+ helper T-cells, which can trigger keratinocyte apoptosis in a manner similar to the way in which the CD8+ lymphocyte/MHC class I interaction activates the process. The presentation of the antigen may stimulate helper T-cells to secrete Th1 cytokines, such as IL-2 and IFN-γ.[23] When IFN-γ is chronically produced from the activated helper T-cells, oral lichen planus can persist in a chronic manner.

Sugerman et al. discusses how some T-cells in the oral lichen planus infiltrate are not specific for the antigen and are not activated; thus, some lymphocytes must be retained within oral lichen planus lesions by other mechanisms.[21] Four mechanisms associated with pre-existing inflammation include the epithelial basement membrane, matrix metalloproteinases, mast cells, and chemokines.[21,23] It is possible that, rather than apoptotic keratinocytes leading to basement membrane disruption, epithelial basement membrane disruption may trigger keratinocyte apoptosis in oral lichen planus.[21] Tsai et al. found that the level of matrix metalloproteinase-2 (MMP-2) is significantly higher in patients with chronic inflammation from oral lichen planus

than in patients without lichen planus.[25] MMP-2 is in the gelatinase family of matrix metalloproteinases and cleaves type IV collagen found in the basement membrane.[21] If increased levels of MMP-2 are found in those with oral lichen planus and MMP-2 cleaves the basement membrane collagen, it can be implied that MMP-2 plays a role in the basement membrane degradation seen in oral lichen planus. In addition to MMP-2, Zhou et al. found that MMP-9 secretion by T cells is greater in lichen planus patients[26]; MMP-9 is another member of the gelatinase family responsible for cleaving type IV collagen.

Sharma et al. found an increase in mast cell count in the oral mucosal biopsies of lichen planus patients when compared to normal controls.[27] In addition, the majority (60%) of the mast cells in oral lichen planus patients are degranulated, compared to only 20% of mast cells degranulated in normal controls.[21] When mast cell degranulation occurs, pro-inflammatory cytokines such as TNF-α, chymase, and tryptase are released leading to the chronic inflammation seen with oral lichen planus.[23] The final factor proposed to be involved in the non-specific inflammatory response in lichen planus is chemokines. RANTES (regulated on activation, normal T cell expressed and secreted) plays an important role in recruiting inflammatory cells and activating mast cell migration and degranulation.[23]

When all of these non-specific mechanisms are combined together, it is realized that many different mechanisms may be involved in the development of oral lichen planus at the immunologic level. RANTES stimulates mast cell degranulation, mast cell chymase activates MMP-9, MMP-9 disrupts the epithelial basement membrane, and the epithelial basement membrane disruption causes keratinocyte apoptosis. It may be one mechanism alone, or it may be several of these mechanisms combined, which causes oral lichen planus.

Some clinicians and researchers have hypothesized that lichen planus may be an autoimmune disease, such as rheumatoid arthritis or lupus. These autoimmune diseases share features of oral lichen planus, such as a chronic nature, typical onset in adulthood, predilection for females, and the presence of cytotoxic T-cells. One of the major arguments for oral lichen planus being an autoimmune disease is that TGF-β1 has been found in lower levels in patients with oral lichen planus.[28] TGF-β1 plays a role in immunosuppression; thus, without its immunosuppressive effects, T cells further proliferate, and cytokines continue to be secreted. In addition to a lack of TGF-β1, the breakdown of immune privilege, keratinocyte apoptosis, and heat shock proteins are other hypotheses that have been proposed, with smaller amounts of available evidence to support them, to implicate autoimmunity as the cause of oral lichen planus.[21]

Lichen planus histologically shows hyperparakeratosis, basal cell layer degeneration, saw-tooth rete ridges, and a band-like infiltrate of lymphocytes in the sub-epithelial layer.[29] The dense band-like infiltrate of lymphocytes, basal cell layer degeneration, and colloid bodies are the key histologic findings of oral lichen planus.[30] Direct immunofluorescence (DIF) can be used to differentiate oral lichen planus from other oral diseases, such as mucous membrane pemphigoid or pemphigus vulgaris. According to a study by Helander and Rogers, the presence of shaggy deposition of fibrin along the basement membrane zone is the best indicator of oral lichen planus with DIF, giving a sensitivity of 70% and a specificity of 78%.[31] These histological findings are related to the proposed pathogenesis of lichen planus mentioned earlier. Specifically, the basal cell layer degeneration caused by a combination of keratinocyte apoptosis, MMP-2 and MMP-9 cleaving the basement membrane collagen, and mast cell degranulation, contribute to the complex pathogenesis of oral lichen planus and its histological correlations.

Once a more complete picture of the pathogenesis of oral lichen planus has been created, it will become easier to appropriately manage oral lichen planus patients. As its pathogenesis is further elucidated, treatment with antibodies to TNF-α and interferon-γ, treatments which stabilize mast cells to prevent mast cell degranulation, or treatment with immunosuppressants which impair T-cell function may all be used to treat lichen planus in the future.[23]

Potential for Malignant Transformation

Patients with oral lichen planus should be educated regarding the relative risk of malignant transformation, although this risk is highly controversial in the literature. A recent review examining 18 retrospective studies and 3 prospective studies found an overall transformation rate of 1.4%.[32] Most retrospective studies with varying inclusion criteria and study design find the frequency of oral cancer among oral lichen planus patients to be between 0% and 5.3%.[33] If a 1% transformation rate of oral lichen planus is chosen, this rate would still be higher than the incidence of oral cancer in the general population, which is estimated to be 0.011% according to the Surveillance, Epidemiology, and End Results Program from the National Cancer Institute.[34]

The erosive and plaque-like forms of oral lichen planus have been particularly associated with malignant transformation.[33] It is also believed that the risk of malignant transformation can be reduced with smoking cessation and decreased alcohol consumption.

Despite evidence in the literature stating the malignant transformation potential of oral lichen planus, many clinicians disagree with the possibility of its potential premalignant nature. Cheng and others described three main reasons why a controversy still exists. First, data reporting is not consistent among published articles, especially in terms of histologic presentation. Next, other oral diseases exist that have similar histologic features to oral lichen

planus; thus, it is difficult to definitively say in these retrospective studies whether the patient had true oral lichen planus or rather a lichen planus mimic such as proliferative verrucous leukoplakia, a condition known to have significant malignant transformation potential. Finally, there is a lack of a universally accepted diagnostic criteria for oral lichen planus, making it difficult to validate studies concluding the malignant transformation potential of oral lichen planus.[1]

Psychological Symptoms in Oral Lichen Planus

Patients' constant pain can result in psychological symptoms, such as irritability, anxiety, and depression. Significantly higher levels of depression, anxiety, and stress have been observed in patients with oral lichen planus compared to patients without mucosal disease.[35, 36] A study by Zucoloto et al. found that an increase in anxious mood levels and anxiety-related physical symptoms is associated with worsening of severity of oral lichen planus.[37] Gavic examined patients with recurrent aphthous stomatitis and oral lichen planus and found that 44% and 50% of patients had positive stress tests, respectively.[38] A recent systematic review found a higher prevalence of depression (31.19%), anxiety (54.76%), and stress (41.10%) in patients with oral lichen planus. In addition, the study found a higher frequency of depression (OR = 6.15), anxiety (OR = 3.51), and stress (OR – 3.64).[39]

Furthermore, there is an economic burden to patients with oral lichen planus, as many patients see multiple healthcare providers to diagnose and manage the disease. A study at Eastman Dental Hospital in the United Kingdom found that the average annual direct cost of oral lichen planus is £398.58, or $540.27.[40] In the United States, this cost is likely even greater, as the UK provides free public health care through the National Health Service to all English residents.

Chaudhary studied stress, anxiety, and depression in patients with oral lichen planus and found significantly higher stress, anxiety, and depression levels in patients with the disease.[41] Additionally, he hypothesized that psychological stressors play an important role in the causation of oral lichen planus. It is clear that patients with oral lichen planus display higher signs of psychological symptoms, and it is likely a two-way relationship; that is, not only is stress a risk factor for oral lichen planus, but oral lichen planus could have a negative effect on stress.

The onset of these psychological symptoms may be due to pain but may also be related to stress from a lack of clear consensus on the etiology, pathogenesis, or treatment of oral lichen planus, resulting in patients being referred from one physician to another, and from one dentist to another.

Current Treatments

Topical corticosteroids are the widely accepted first-line therapy for symptomatic oral lichen planus,[42] with clobetasol[43] and fluocinonide[44] being the most commonly prescribed. In a 2009 randomized controlled trial comparing two concentrations of clobetasol, 93% of patients using a 0.025% concentration and 87% of patients using a 0.05% concentration reported symptom improvement, and 87% of the 0.025% concentration and 73% of the 0.05% concentration group showed clinical signs of improvement.[45] In a 1993 double-blind, placebo-controlled clinical study using fluocinonide in an adhesive base, 60% had a good response to treatment and 20% showed complete remission; however, 20% showed no response to fluocinonide therapy.[46]

Non-steroid immunosuppressants, such as pimecrolimus,[47] tacrolimus,[48] and cyclosporine[49] have also been used with some degree of success. A 2008 prospective randomized double-blind vehicle-controlled study examined the efficacy of pimecrolimus cream 1%

compared to a vehicle cream and found that 70% of patients in the pimecrolimus group had complete clearing of oral lichen planus erosions, with a significant decline in meal-triggered pain and continuous pain detected by Visual Analogue Scale (VAS).[50] A retrospective study in 2014 evaluated 21 patients treated with 0.1% topical tacrolimus and found 33% had complete remission at 6 to 7 months.[51] However, a 2021 systematic review and meta-analysis concluded that there is not sufficient evidence that tacrolimus is more effective than corticosteroids in treatment of oral lichen planus, and it may be more likely to cause adverse effects.[52] A 1995 study found that participants who rinsed with 5 ml (500 mg) of cyclosporine for 5 minutes each day for four weeks appeared to have decreased pain, lesion size, and severity of oral lichen planus.[53] Rituximab is a monoclonal antibody approved for the treatment of rheumatoid arthritis and some cancers. A case report by Heelan and others in 2015 described complete remission of a woman's oral lichen planus after two 1 g doses of rituximab two weeks apart.[54]

Unfortunately, topical steroid or other immunosuppressant treatment of oral lichen planus is often associated with local adverse effects, especially candidosis.[55] Candida overgrowth requires treatment with antifungal agents, such as nystatin rinse of clotrimazole lozenges. Furthermore, Gonzalez-Moles and Scully described substantial inhibition of the hypothalamus-pituitary-adrenal (HPA) axis during initial treatment of oral lichen planus with an aqueous solution of 0.05% clobetasol, which may lead to an impaired stress response and immunosuppression.[56] More seriously, some have suggested a connection between tacrolimus treatment and development of oral squamous cell carcinoma; thus, patients should be monitored closely if using tacrolimus topically as a treatment for oral lichen planus.[57]

Due to these side effects, researchers have begun to study other treatments thought to have less side effects. In a case series by Cafaro and others, performing low-level laser therapy

(LLLT) using a 980-nm gallium-aluminum-arsenide (GaAIAs) diode laser on oral lichen planus lesions resulted in complete resolution of clinical signs in 78% of oral lichen planus lesions and partial resolution in 17% of lesions. No adverse effects of LLLT were noted in the study.[58]

Purslane, a succulent plant rich in antioxidants and other compounds, was studied in a 2009 randomized double-blind placebo-controlled trial; approximately 83% of purslane patients showed partial to complete remission, with a significant decrease in VAS scores noted for purslane patients. No adverse effects of purslane were noted in the study.[60] Topical tocopherol, an essential vitamin and powerful antioxidant, has been studied as well, specifically in a cohort of patients with reticular oral lichen planus. While significant differences were seen between the placebo and tocopherol groups in the surface area of the lesions, no significant differences were noted in VAS scores or length of striae. No patients reported adverse effects throughout the course of treatment.[61]

Despite the widespread use of some of these treatment modalities, a recent Cochrane Review declared a low confidence in the finding that topical corticosteroids may be more effective than placebo for reducing pain in symptomatic oral lichen planus and a very low confidence that immunosuppressants may be more effective than topical corticosteroids.[33] Thus, more research is needed to determine a treatment for oral lichen planus that is effective in not only reducing patient symptoms, but also in reducing clinical signs of disease with minimal adverse effects.

Reactive Oxygen Species, Oxidative Stress, and Antioxidants

Reactive Oxygen Species and Oxidative Stress

Reactive oxygen species (ROS) are molecules which typically originate from the electron transport chain of the mitochondria.[62] As electrons transfer down the electron transport chain, some electrons leak away and cause the reduction of oxygen into superoxide.[63] Superoxide radicals, hydrogen peroxide, hydroxyl radicals, and singlet oxygen are examples of ROS. At normal levels, ROS are important in many cell processes such as cell growth, differentiation, and death, but when ROS levels increase, adverse effects can be seen.[64] High levels of ROS have been found to play a pivotal role in the development of human diseases, such as cancer, diabetes, and autoimmune conditions.[65]

The mechanism in which high levels of ROS can be detrimental to human health is through a process called oxidative stress.[64] Oxidative stress was first described by Sies in 1985 as "a disturbance in the prooxidant-antioxidant balance in favor of the former."[66] In times of oxidative stress, lipid oxidation can occur which is an important step in the development of atherosclerosis. In addition, protein oxidation is often noted, leading to decreased protein turnover, gene transcription, and cell integrity. Finally, oxidative stress can cause DNA oxidation, leading to mutagenesis and potentially to cancer and cell aging.[67]

Antioxidants

Antioxidants are substances that can counteract oxidative stress and lessen the effect of oxidative stress in human health.[64] When present, antioxidants can prevent or delay the damage that ROS cause by slowing the oxidation of the substrate.[68] While the human body possesses

many of its own natural antioxidant defenses, protection against ROS can be improved by intake of dietary antioxidants.[69]

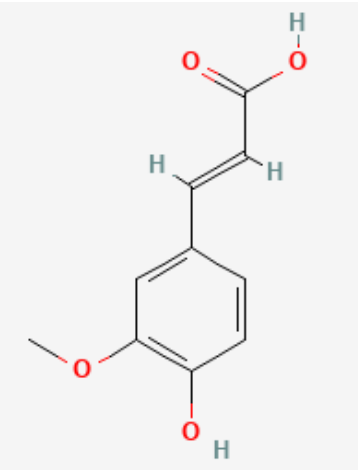
Although synthetic antioxidants exist, many antioxidants can be found naturally in plant products such as fruit, vegetables, seeds, nuts, and more.[69] Vitamins A, E, C, B3, B2, B3, B6, and B12 have been known to have antioxidant properties, as well as some fats and lipids, amino acids, peptides and proteins, minerals, and enzymes.[70] However, it has been shown that many phenols and polyphenols are stronger antioxidants than the vitamin antioxidants [71] ; thus, using antioxidants to focus on the reversal of oxidative stress often focuses on phenols and polyphenols.

Phenolic compounds are the largest group of secondary metabolites in plants and can vary in structure. However, most phenolic compounds are characterized by the presence of an aromatic ring having one or more hydroxy- components.[72] Phenolic acids can be divided into cinnamic acid derivatives and benzoic acid derivatives, with the cinnamic acid derivatives being more effective antioxidants than the corresponding benzoic acid derivatives. This is due to the differing structures of each, as cinnamic acids have conjugation through the double bonds of the ring, enhancing their ability to stabilize free radicals and act as antioxidants.[69]

One of the most common phenolic compounds is ferulic acid (Figure 1).[73] Ferulic acid is known to have anti-inflammatory, anti-cancer, antibacterial, and anti-wrinkle effects in humans,[74] and is most commonly found in rice, wheats, and grains.[75] The antioxidative capacity of ferulic acid is credited to its single hydroxy- group which is para-substituted on the aromatic ring connected to the conjugated side chain; the para substitution results in the molecule's stabilization. The ortho substitution of a methoxy-group further increases the stability of ferulic

acid, thus increasing its antioxidative potential.[76] In addition to an antioxidant effect, ferulic acid has also been noted to have an anti-inflammatory effect.[77]

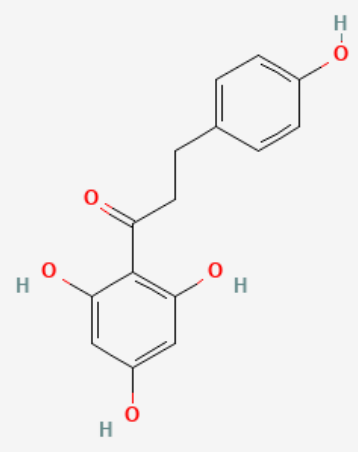
Figure 1. Ferulic Acid Chemical Structure



Flavonoids are polyphenolic compounds which act as effective antioxidants and are found in fruit, vegetables, teas, red wine, and chocolate.[78] The structure of flavonoids includes two aromatic rings linked by a three-carbon aliphatic chain.[69] Like ferulic acid, the antioxidative potential of flavonoids lies in their structure, specifically the 3',4'-dihdroxy structure in the B-ring.[78]

Phloretin (Figure 2) is a flavonoid of the dihydrochalcone class and is most commonly found in apples.[79] Chalcones lack heterocyclic C rings and are known for their anti-inflammatory, anti-cancer, and antibacterial effects similar to polyphenolic compounds. Specifically, phloretin acts as an inhibitor to lipid peroxidation and peroxynitrite scavenging.[80] Additionally, phloretin's anti-inflammatory activity decreases levels of cytokines and expression of COX-2, thus leading to a reduction in prostaglandin E_2 and nitric oxide levels.[79]

Figure 2. Phloretin Chemical Structure



Lichen Planus, Oxidative Stress, and Antioxidants

Studies have shown that oxidative stress markers are elevated in the saliva of oral lichen planus (OLP) patients. In a 2017 cross-sectional study of unstimulated saliva in patients with oral lichen planus and healthy controls, the mean value of superoxide dismutase (SOD), the first line defense against reactive oxygen species, was 1.23 ± 0.34 in patients with OLP, whereas in the control group it was 0.54 ± 0.26 U/mL; the mean value of malondialdehyde (MDA), an indicator of lipid peroxidation, was 1.42 ± 0.30 in OLP patients, but was 0.86 ± 0.14 in the control group. Both differences were statistically significant.[81] The higher levels of SOD and MDA indicate greater levels of oxidative stress in patients with OLP compared to healthy controls.

Another study from 2008 showed decreased levels of the major antioxidant in saliva, uric acid, in patients with OLP. In healthy controls, salivary uric acid level approximate 3.4 mg/dl, but in OLP patients, it only approximated 2 mg/dl, a statistically significant difference.[82] The lower uric acid levels in patients with OLP may be because of increased levels of oxidative stress in these patients.

Higher levels of nitrite and nitric oxide have also been found in patients with oral lichen planus when compared to healthy controls. Tvarijonaviciute and others found that nitric oxide levels averaged 145.7 μmol in OLP patients and 17.85 μmol in control patients; nitrite levels averaged 141.0 μmol in OLP patients and 22.02 μmol in control patients. Both differences were statistically significant.[83]

As mentioned earlier in this review, one of the histologic hallmarks of oral lichen planus is basal cell layer degeneration of the epithelium, which might be attributed to lymphocytic infiltration. This infiltration can lead to cytokine production, which, in turn, can leads to production reactive oxygen species (ROS). Thus, it may be hypothesized that oxidative stress and ROS play an important role in the OLP disease process.[84]

Antioxidants and Healing

Combinations of antioxidants have been used to treat patients with arthritis, cancer, diabetes, atherosclerosis, and neurodegenerative diseases.[65] Curcumin, a yellow pigment found in turmeric, has been used to treat knee osteoarthritis. A 2014 randomized double-blind placebo-controlled trial found that patients treated with curcuminoids had greater reductions in an osteoarthritis index, pain on a visual analogue scale, and Lequesne's pain functional index compared to patients given placebo.[85]

In a study evaluating the population of Linxian China, which has some of the highest rates of esophageal carcinoma and gastric carcinoma in the world, it was found that participants who received a combination of beta-carotene, alpha-tocopherol, and selenium had significant reductions in total mortality and cancer mortality.[86] Thus, the use of combined antioxidants may be helpful in reducing cancer risk.

In patients with Type 2 diabetes, patients given aqueous cinnamon extract had a significant reduction in plasma glucose after four months of treatment compared to a placebo group. The reduction in the cinnamon group was 10.3%, whereas the reduction in plasma glucose in the placebo group was only 3.4%.[87] Cinnamon extracts are often used as antioxidants.

In dentistry, antioxidant combinations have been applied topically for the treatment of xerostomia and aphthous ulcers, to reduce gingival inflammation in orthodontic patients with gingivitis, and to promote healing after periodontal and oral surgery. In a 2021 clinical trial, patients suffering from radiation-induced xerostomia were given a placebo tablet or Aqualief, tablets with two antioxidants, carnosine and dried calcyes of Hibiscus sabdariffa. In patients receiving the active gel, there was a significantly higher salivary flow rate than when compared to patients receiving a placebo gel.[88] Thus, antioxidants may be used to help reduce dryness in patients suffering from xerostomia.

In Thailand, plant-based remedies have long been used for treating aphthous ulcers, specifically extracts from the plants *Quercus infectoria, Kaempferia galanga, Coptis chinesis*, and *Glycyrrhiza uralensis* have been used, each of which have antioxidant potential except *K. galanga*. In a laboratory study in Thailand, it was observed that an aphthous powder containing extracts from the four plants mentioned previously is an effective treatment for aphthous ulcers.[89]

A 2016 randomized controlled trial evaluating an antioxidant-essential oil gel as a treatment for gingivitis in orthodontic patients found statistically significant reductions in bleeding on probing (21.8%) and gingival index (9.0%). In addition to the antioxidants in the gel, the essential oil component of the gel may play a role. While not statistically significant, orthodontic patients using the antioxidant-essential oil gel showed reduction in probing depths compared to the placebo group.[90]

Chapple and others performed a study in 2012 to determine whether dietary supplementation with foods known to contain systemic antioxidants would improve treatment outcomes in patients undergoing non-surgical periodontal therapy. They concluded that in adults with chronic periodontitis, there are minor gains in clinical attachments levels during the initial phases of treatment when dietary supplementation with systemic antioxidants is used.[91]

A 2010 in vitro study found that phloretin and ferulic acid can mitigate the effects on oral fibroblasts caused by reactive oxygen species from nicotine, alcohol, and hydrogen peroxide.[92] Furthermore, carefully controlled mixtures of bioactive antioxidants have promoted the proliferation and migration of human oral fibroblasts.[93]

Essential Oils

Mouthrinses containing essential oils have a long-standing use in dentistry and have been demonstrated to be effective in reducing plaque and achieving healthy gingival tissue.[94] A 2015 meta-analysis published in the Journal of the American Dental Association found greater improvements in gingival tissue and reduced plaque and gingivitis in patients who used essential-oil mouthrinses, compared to those who used only mechanical methods for plaque control.[95]

Recently, essential oils have also been used to treat oral diseases. For example, an oral rinse containing thyme and peppermint oil was found to prevent or reduce symptoms of oral mucositis in patients undergoing chemotherapy.[96] A more recent study compared the use of a non-aromatic very rich in steranes (NAVS) naphthalan to traditional topical steroid in the treatment of oral lichen planus and recurrent aphthous stomatitis. The researchers found no

difference between groups treated with topical steroids versus the essential oil group and concluded that NAVS naphthalan may be an alternative intervention for treatment of patients with oral lichen planus or recurrent aphthous stomatitis.[97]

Current Study

As a recent Cochrane review stated that there is a low level of confidence that the first line treatment for oral lichen planus, topical corticosteroids, is more effective than a placebo[61,] it is necessary to continue research to assess the most efficacious treatment for this disease. Current findings suggest that a topical gel containing antioxidants and essential oils may provide satisfactory relief for oral lichen planus symptoms. The purpose of this study is to determine whether a gel containing the antioxidants phloretin and ferulic acid, as well as the essential oils menthol, peppermint oil, thyme, sage oil, and clover flower oil, modifies the signs and symptoms of oral lichen planus.

The primary endpoint is change in discomfort reported using VAS. The VAS is a widely used scoring system due to its simplicity, and its acceptability as a measure for discomfort has been shown since the 1970s.[98] Studies have shown that no clinically relevant difference exists between a paper-based VAS assessment and a digital VAS assessment.[99] The secondary endpoints include change in oral health-related quality of life (OHRQoL) measured as an overall score on Dugas' modification of the Oral Health Impact Profile (OHIP)[100] and change in clinical severity of disease measured as an overall score using Piboonniyom's reticular-erythematous-ulcerative (REU) scoring system.[101] The OHIP was created in 1994 to conceptualize the social impacts arising from oral conditions. Dugas' modified version narrowed the OHIP's total items

from 49 to 17 and is measured on a five-point Likert-scale.[102] The categories include questions on functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap.

Piboonniyom's REU scoring system divides the oral cavity into ten sites and the severity of lesions at each location are scored based on the presence or absence and the size of the lesion. For reticular/hyperkeratotic lesions, sites are scored as 0 if no white striations are present but scored as 1 if there is a presence of white striations of keratotic papules. For erythematous/ erosive lesions, a score of 0 is given is there is no lesion, a score of 1 is given if a lesion is present less than 1 cm^2, a score of 2 is given if a lesion is present and ranges from 1 to 3 cm^2, and a score of 3 is given for lesions larger than 3 cm^2. Ulcerative areas are scored from 0 to 3 using the same measurements of area of involvement as the erythematous/erosive areas. A total weighted REU score is calculated by adding the sum of the reticular lesions + the sum of the erythematous lesions X 1.5 + the sum of the ulcerative lesions X 2.0 ($\sum R + \sum(E \times 1.5) + \sum(U \times 2.0)$).[101]

MATERIALS AND METHODS

Protocol Approval

The Institutional Review Board of Texas A&M University College of Dentistry (TAMUCOD), Dallas, Texas, reviewed and approved the protocol for this randomized, double-blind, placebo-controlled study. (IRB ID: IRB2021-0242-CD-FB).

Patient Enrollment

Patients were recruited to participate in the study from the new or current patient population of Texas A&M University College of Dentistry in Dallas, Texas or from the new or current patient population of Dr. Jacqueline Plemons' private practice in Dallas, Texas. Patients were contacted via telephone, by email, or at in-person visits to request study participation.

Inclusion criteria included: (1) documented diagnosis of oral lichen planus, lichenoid mucositis, or chronic mucositis with lichenoid features via biopsy confirmation by a board-certified oral pathologist prior to entry into the study, (2) persistent signs and/or symptoms of oral lichen planus, (3) currently exhibiting the atrophic, ulcerative, or erosive form of oral lichen planus and is currently experiencing discomfort from the condition, (4) ability to provide verbal and written informed consent, and (5) ability to use electronic tablet to take electronic surveys.

Exclusion criteria included: (1) patients under the age of 18, (2) women who are pregnant or breastfeeding, (3) allergy to any ingredients in the gel (phloretin, ferulic acid, menthol peppermint oil, thyme, sage oil, clove flower oil, xylitol), (4) uncontrolled systemic disease that

compromises the immune system of the patient, e.g. diabetes, AIDS, etc., (5) current smoker, (6) past or current use of any topical antioxidant therapy, (7) prisoner, and (8) non-English speaker.

Procedures

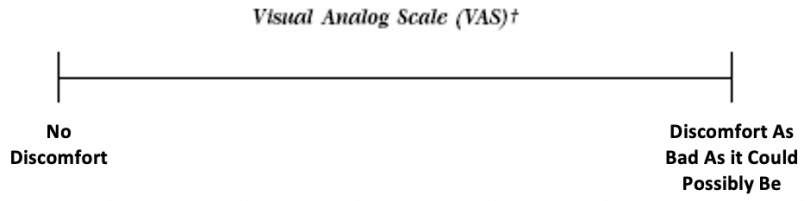
Patients who met the inclusion criteria of the study signed an informed consent document prior to admission into the trial. A fully executed copy of the consent document was provided to the participant and the original maintained by the investigators.

After enrollment, patients were randomly assigned to one of two groups, an active gel group or an inactive placebo gel group. The active gel was a ticalose gum gel which contains two antioxidants, phloretin and ferulic acid, plus antimicrobials menthol and thymol, as well as xylitol, sage oil, and clove flower oil. The placebo was a ticalose gum gel containing only xylitol without the antioxidants and natural antibacterial agents. Flavoring agents in the ticalose gum ensured that the active gel and the placebo gel were indistinguishable. The company who provided the gel sent the active gel and the placebo gel in two separate boxes, one labelled “A” and one labelled “B.” The study investigators were blinded as to which “A” or “B” was the active or the placebo gel. All tubes were identical. A randomly generated listed was created in Excel to follow the order in providing the “A” or “B” gel to each patient. Gels were distributed in the order determined as patients presented to their baseline appointment.

At the initial visit, patients first signed consent forms. Next, patients took electronic surveys through Texas A&M University Qualtrics on an electronic tablet (Windows Surface Pro). The first survey collected demographic data for each participant, including age, sex, race, and ethnicity. The second survey (Figure 3) was a Visual Analog Scale (VAS), where patients

used their finger to drag the pointer to their current level of discomfort on a line with measures from 0 to 100. A score of 0 indicated the patient had “no discomfort”, whereas a score of 100 indicated “discomfort as bad as it possibly could be.” Thus, a higher score indicated greater discomfort.

Figure 3. Visual Analog Scale (VAS)



The third survey (Figure 4) taken at baseline was a modification of the Oral Health Impact Profile (OHIP) as proposed by Dugas et al. in 2002. This survey sought to assess the impact on oral health-related quality of life (OHRQoL) among study participants.

Figure 4. Oral Health Impact Profile (OHIP) Administered at Baseline

	Never	Hardly Ever	Occasionally	Fairly often	Very often
Functional limitation					
-Have you had trouble pronouncing words because of your teeth and mouth?	0	1	2	3	4
-Have you felt that your sense of taste has worsened because of your teeth or mouth?	0	1	2	3	4
Physical pain					
-Have you had painful aching in your mouth?	0	1	2	3	4
-Have you found it uncomfortable to eat any foods because of your teeth or mouth?	0	1	2	3	4
-Have you had to alter the temperature of the foods that you eat because of your teeth or mouth?	0	1	2	3	4
Psychological discomfort					
-Have you been self-conscious because of your teeth or mouth?	0	1	2	3	4
-Have you felt tense because of your teeth or mouth?	0	1	2	3	4
Physical disability					
-Has your diet been unsatisfactory because of your teeth or mouth?	0	1	2	3	4
-Have you had to interrupt meals because of your teeth or mouth?	0	1	2	3	4
Psychological disability					
-Have you found it difficult to relax because of your teeth or mouth?	0	1	2	3	4
-Have you found it difficult to fall asleep because of your teeth or mouth?	0	1	2	3	4
-Have you ever been awakened by problems with your teeth or mouth?	0	1	2	3	4
-Have you been embarrassed because of your teeth or mouth?	0	1	2	3	4
Social disability					
-Have you been irritable with other people because of your teeth or mouth?	0	1	2	3	4
-Have you had difficulty doing your usual jobs because of problems with your teeth or mouth?	0	1	2	3	4
Handicap					
-Have you felt that life in general was less satisfying because of your teeth or mouth?	0	1	2	3	4
-Have you been totally unable to function because of your teeth or mouth?	0	1	2	3	4

After patients completed electronic surveys, a standardized series of thirteen intraoral photographs were taken of the patient's mouth to provide a clinical presentation of the patient's current oral lichen planus condition. Photos included: (1) upper lip, (2) lower lip, (3) right buccal

mucosa, (4) left buccal mucosa, (5) dorsal tongue, (6) right ventral tongue, (7) left ventral tongue, (8) floor of mouth, (9) soft palate, (10) hard palate mucosa, (11) maxillary gingiva, (12) mandibular gingiva, (13) maxillary and mandibular gingiva with patient in occlusion. These photos were taken in order to be able to score the patient's clinical severity of disease using Piboonniyom's 2005 REU scoring system (Figure 5). Two investigators, AR and JP, completed a calibration exercise. After calibration, each investigator examined the clinical photographs of each patient and scored photographs based on the REU scoring system.

Figure 5. REU Scoring System

Site	Reticular Area		Erythematous Area				Ulcerative Area			
Upper/lower labial mucosa	0	1	0	1	2	3	0	1	2	3
Right buccal mucosa	0	1	0	1	2	3	0	1	2	3
Left buccal mucosa	0	1	0	1	2	3	0	1	2	3
Dorsal tongue	0	1	0	1	2	3	0	1	2	3
Ventral tongue	0	1	0	1	2	3	0	1	2	3
Floor of mouth	0	1	0	1	2	3	0	1	2	3
Hard palate mucosa	0	1	0	1	2	3	0	1	2	3
Soft palate/tonsillar pillars	0	1	0	1	2	3	0	1	2	3
Maxillary gingiva	0	1	0	1	2	3	0	1	2	3
Mandibular gingiva	0	1	0	1	2	3	0	1	2	3
Total										

After completion of consent, electronic surveys, and photographs, participants were provided detailed study instructions (verbal and written). Patients were asked not to undergo dental cleaning during the study period and were instructed to brush twice daily (morning and evening) for at least one minute with an ultra-soft toothbrush and a non-tartar control and non-whitening toothpaste (Crest Kids Sparkle) that was provided to each participant. Patients were asked not to use mouthwash during the study period and were asked to rinse vigorously with water only for 30 seconds after finishing brushing. Patients were asked to apply the gel three times daily: 30 minutes after brushing in the morning, mid-day after eating, and just before bed

(at least 30 minutes after brushing). Patients were directed to apply the gel to areas of involvement and distribute the product in the mouth using the tongue only. Patients were directed not to eat or drink for 30 minutes after applying the gel. After reviewing the study instructions, patients were provided the randomly assigned gel, a toothbrush, and toothpaste and were dismissed and re-appointed four weeks later.

At the four-week and eight-week appointments, patients completed the same VAS administered at baseline and had the same series of intraoral photographs taken; however, the OHIP slightly differed at the four-week and eight-week appointments, as patients only indicated whether their symptoms improved, worsened, or stayed the same (Figure 6).

Figure 6. OHIP Administered at 4 Weeks and 8 Weeks

The following questions were asked to you at the beginning of the treatment period, to which you answered, "never", "hardly ever", "occasionally", "fairly often", or "very often". Please review the following questions again and indicate whether each item has, improved, worsened, or stayed the same.

Functional limitation			
-Have you had trouble pronouncing words because of your teeth and mouth?	Improved	Worsened	Stayed the same
-Have you felt that your sense of taste has worsened because of your teeth or mouth?	Improved	Worsened	Stayed the same
Physical pain			
-Have you had painful aching in your mouth?	Improved	Worsened	Stayed the same
-Have you found it uncomfortable to eat any foods because of your teeth or mouth?	Improved	Worsened	Stayed the same
-Have you had to alter the temperature of the foods that you eat because of your teeth or mouth?	Improved	Worsened	Stayed the same
Psychological discomfort			
-Have you been self-conscious because of your teeth or mouth?	Improved	Worsened	Stayed the same
-Have you felt tense because of your teeth or mouth?	Improved	Worsened	Stayed the same
Physical disability			
-Has your diet been unsatisfactory because of your teeth or mouth?	Improved	Worsened	Stayed the same
-Have you had to interrupt meals because of your teeth or mouth?	Improved	Worsened	Stayed the same
Psychological disability			
-Have you found it difficult to relax because of your teeth or mouth?	Improved	Worsened	Stayed the same
-Have you found it difficult to fall asleep because of your teeth or mouth?	Improved	Worsened	Stayed the same
-Have you ever been awakened by problems with your teeth or mouth?	Improved	Worsened	Stayed the same
-Have you been embarrassed because of your teeth or mouth?	Improved	Worsened	Stayed the same
Social disability			
-Have you been irritable with other people because of your teeth or mouth?	Improved	Worsened	Stayed the same
-Have you had difficulty doing your usual jobs because of problems with your teeth or mouth?	Improved	Worsened	Stayed the same
Handicap			
-Have you felt that life in general was less satisfying because of your teeth or mouth?	Improved	Worsened	Stayed the same
-Have you been totally unable to function because of your teeth or mouth?	Improved	Worsened	Stayed the same

After the four-week appointment, patients were provided a new toothbrush, toothpaste, and new bottle of the same randomly assigned gel and were appointed four weeks later for a final appointment after eight total weeks of using the gel. At the final eight-week appointment,

participants took a final survey instrument (Figure 7) that perceived satisfaction on six aspects of the gel product using a simple five-point Likert scale from “very satisfied” to “very unsatisfied.”

Figure 7. Patient Satisfaction Survey

How satisfied are you with	Very Satisfied	Satisfied	Neutral	Unsatisfied	Very Unsatisfied
1. The time it took to feel relief					
2. The confidence in your breath now compared to your confidence in your breath at the start of the study					
3. Your ability to eat spicy, acidic, and rough-textured foods now compared to before using the test gel in this study					
4. How comfortable do you feel while brushing your teeth now compared to the start of the study					
5. How your gums/tongue/cheeks look now compared to the start of the study					
6. How your gums/tongue/cheeks feel now compare to the start of the study					

Patient email addresses were collected at the completion of the study in order to send a link for the patient to redeem two free bottles of the active gel as a thank you for their participation in the study.

Statistical Methods

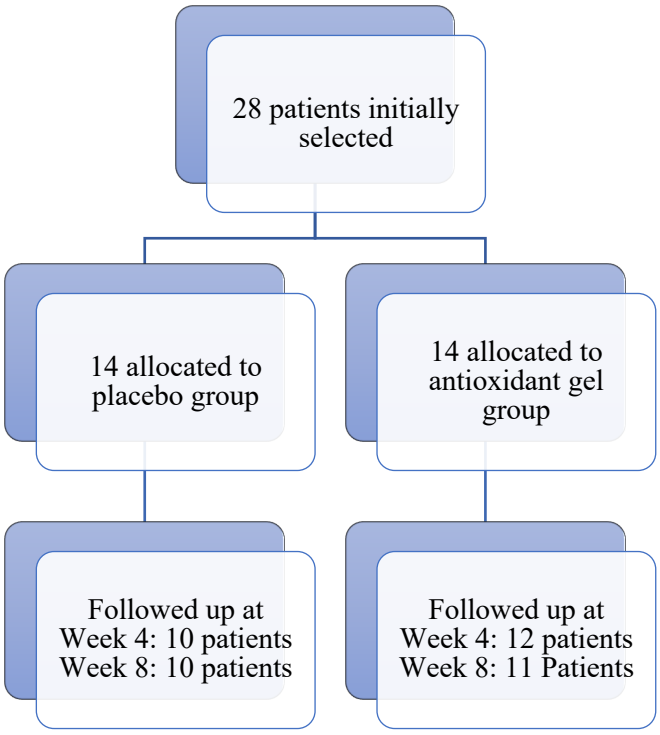
SPSS version 28 (SPSS Inc.; Chicago, IL) was used to analyze the data, using $p<0.05$ significance level. To describe patient demographics, medians and first and third quartiles (Q1 and Q3) were used; the non-normality of the distribution was verified via Kolmogorov-Smirnov tests, so differences between medians were tested using Kruskal-Wallis tests.

Mean and standard deviation were used as descriptive statistics for the variables of interest. However, considering the small sample size, an assessment of normality across dependent variables of interest was important for selecting an appropriate statistical method. A Shapiro-Wilk test was performed for VAS and REU dependent variables. Results indicated scores significantly departed from normality ($p <0.05$). Based upon these results, the Mann-Whitney U test was deemed appropriate to evaluate differences between the control and treatment groups, and the Wilcoxon signed ranks test was used to evaluate differences between time points within the groups. One patient dropped out after 4 weeks, but the patient's data was still included to evaluate 4-week data; the patient was not included in 8-week data.

RESULTS

Twenty-eight patients (21 females, 7 males; mean age 65.93) qualified and consented to be in the study, with 14 patients randomly assigned to each group. Six total patients discontinued the study prior to the 4-week appointment (4 in the placebo group due to uncontrolled continue discomfort and 2 in the antioxidant gel group due to contracting COVID-19). The remaining 22 (18 females, 4 males; mean age 65.68) patients completed 4 weeks, with one additional dropout in the antioxidant gel group at 4 weeks due to lack of symptom control. Figure 8 reports the flow diagram for patients' recruitment.

Figure 8. Flow of Subjects through Each Phase



Of the 22 participants who completed at least four weeks of treatment, 21 reported being white (95.45%) and 1 reported being black (4.55%). Two (9.09%) identified as Hispanic or Latino, whereas 20 (90.91%) reported being not Hispanic or Latino. The mean age of participants in Group A was 60.30 years, whereas the mean age of participants in Group B was 70.17 years. Participant characteristics are described in Table 1.

Table 1. Demographics of Participants at Baseline

	Group A (N=10)	Group B (N=12)	p
Age (years)	57.00 [51.75; 74.25][a]	69.50 [63.50; 74.00][a]	0.1308[b]
Range (years)	29-86	58-87	
Gender (M/F)	2/8	2/10	

[a]Median [Q1;Q3]
[b]Kruskal-Wallis test

Discomfort

At the initial examination, VAS scores were 41.25 ± 26.15 and 45.50 ± 29.43 in the treatment and placebo groups, respectively (Figure 9). The difference between groups was not statistically significant at baseline (p=0.869) (Table 2). From baseline to 4 weeks, the treatment group showed a statistically significant (p=0.028) 27.50 ± 23.76 change in discomfort (measured on VAS) compared to a statistically insignificant (p=0.114) 33.40 ± 21.32 change in the placebo group (Table 2) (Figure 9); the VAS scores between the treatment and placebo groups were not statistically significant at 4 weeks (p=0.530) (Table 2). At the final examination (8 weeks), VAS scores were 18.91 ± 8.35 and 41.70 ± 26.35 in the treatment and placebo groups, respectively, leading to a statistically significant difference (p=0.040) in final VAS score between groups. From baseline to 8 weeks, the treatment group showed a statistically significant (p=0.010)

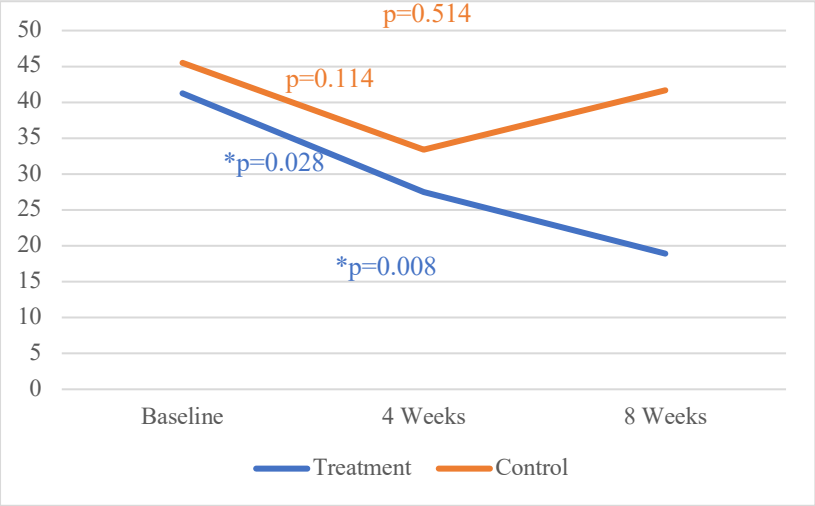
change in discomfort compared to a statistically insignificant (p=0.514) change in the placebo group.

Table 2. VAS Score Data for Baseline, 4 Weeks, and 8 Weeks

VAS	Baseline	4 Weeks	8 Weeks
Treatment	41.25 ± 26.15	27.50 ± 23.76	18.92 ± 7.96
Control	45.50 ± 29.43	33.40 ± 21.32	41.70 ± 26.35
P-Value	0.869	0.530	0.040*

*Mann-Whitney U test ; $p < 0.05$

Figure 9. Level of Discomfort (on VAS)



*Wilcoxon Signed Ranks Test ; $p < 0.05$

Oral Health Impact Profile

The proportion of subjects reporting "some impact" prior to treatment for one or more items in each of the seven subscales of oral health is presented in Table 3. All subjects (100%) had experienced some form of "physical pain" at baseline. In contrast, only 63.63% of subjects experienced any form of "social disability." "Psychological discomfort" was reported

significantly more in females (100%) than in males (75%) ($p = 0.030$). "Physical disability" was also reported significantly more by females (100%) than males (25%) ($p < 0.001$).

Table 3. Prevalence of "Some Impact" Reported for One or More Items in Each Quality of Life Subscale (n = 22)

Subscale	Prevalence (%)		
	Overall	Male	Female
Functional limitation	77.27	75	77.8
Physical pain	100	100	100
Psychological discomfort	95.45	75	100*
Physical disability	86.36	25	100*
Psychological disability	100	100	100
Social disability	63.63	50	66.7
Handicap	77.27	75	77.8

*Pearson Chi-square; $p < 0.05$

At baseline, 95.5% of participants reported "painful aching" and "uncomfortable to eat." In addition, 95.5% of participants reported being "self-conscious" and 90.9% found it "difficult to relax" because of their current oral condition. "Uncomfortable to eat" had a mean impact value of 3.05, which exceeded the 3 score (fairly often) level. "Painful aching," "alter the temperature of foods," "self-conscious," "tense," and "diet unsatisfactory" had mean impact values of 2 or above, meeting the 2 score (occasionally) level. "Unable to function" had the lowest mean impact value (0.55) (Table 4).

There were no statistically significant differences between the placebo and treatment groups for any of the subscale items percentage reporting improvement at 4 weeks. The greatest amount of improvement occurred in the "trouble pronouncing words," "uncomfortable to eat," and "interrupt meals" categories, with 33.3% of participants in the treatment group who reported some impact at baseline reporting improvement in these items at 4 weeks. 0% of treatment group participants who reported being "unable to function" at baseline reported improvement (Table 4).

At 8 weeks, there were statistically significant changes between the placebo and treatment groups in the subscale items for “trouble pronouncing words” (p = 0.046) and for “painful aching” (p = 0.025). Only four subscale items had patients reporting improvement in the placebo group, whereas all seventeen subscale items had patients reporting improvement in the treatment group (Table 4).

Table 4. Prevalence of “Some Impact,” “Mean Impact Value,” and Percentage of Improvement by Treatment Group

Subscale and Item	Prevalence % (n)	Mean Impact Value	Of those reporting "some impact"; % improved by group at 4 weeks			Of those reporting “some impact”; % improved by group at 8 weeks		
			Placebo	Treatment	P-Value*	Placebo	Treatment	P-Value*
Functional limitation								
Trouble pronouncing words	54.5 (12)	1.05	16.7	33.3	0.505	0	50	**0.046**
Sense of taste worsened	68.2 (15)	1.45	0	25	0.155	0	37.5	0.070
Physical pain								
Painful aching	95.5 (21)	2.23	10	27.3	0.314	0	40	**0.025**
Uncomfortable to eat	95.5 (21)	3.05	10	33.3	0.193	10	36.4	0.157
Alter the temp. of foods	90.9 (20)	2.23	10	20	0.531	0	22.2	0.115
Psychological discomfort								
Self-conscious	95.5 (21)	2.00	10	18.2	0.593	0	30	0.060
Tense	86.4 (19)	2.32	11.1	20	0.596	0	33.3	0.058
Physical disability								
Diet unsatisfactory	86.4 (19)	2.00	11.1	30	0.313	11.1	33.3	0.257
Interrupt meals	81.8 (18)	1.64	11.1	33.3	0.257	0	33.3	0.058
Psychological disability								
Difficult to relax	90.9 (20)	1.82	10	30	0.264	0	30	0.060
Difficult to fall asleep	77.3 (17)	1.23	11.1	25	0.453	11.1	37.5	0.200
Awakened	72.7 (16)	1.36	12.5	25	0.522	12.5	50	0.106
Been embarrassed	77.3 (17)	1.55	12.5	22.2	0.6	0	37.5	0.055
Social disability								
Irritable with others	59.1 (13)	0.95	20	25	0.835	0	37.5	0.118
Difficulty doing jobs	54.5 (12)	0.73	20	28.6	0.735	0	50	0.064
Handicap								
Life unsatisfying	77.3 (17)	1.50	14.3	20	0.761	0	33.3	0.090
Unable to function	36.4 (8)	0.55	20	0	0.408	0	33.3	0.134

*Pearson Chi-square (p < 0.05)

The mean quality of life "improvement score" was 3.33 ± 6.39 for the treatment group and 1.600 ± 5.060 for the placebo group at 4 weeks, with no statistically significant difference between the two groups. At 8 weeks, the mean quality of life "improvement score" was 3.27 ± 5.85 in the treatment group and 0.30 ± 0.67 for the control group.

Clinical Severity

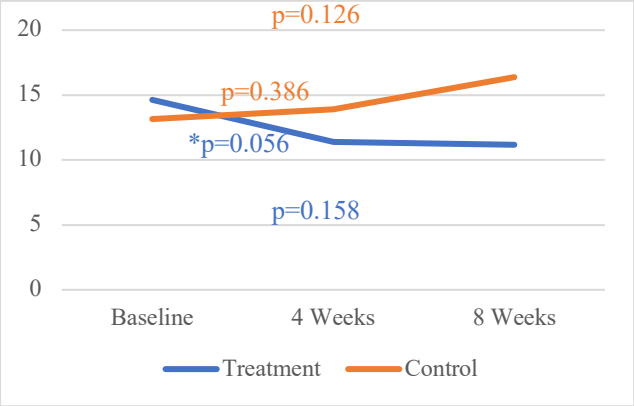
At the initial examination, REU score was 13.00 ± 13.99 and 11.65 ± 8.46 in the treatment and control groups, respectively. The groups were not significantly different ($p = 0.974$). At 4 weeks, the REU score was 9.46 ± 5.68 and 11.25 ± 8.20 in the treatment and control groups, respectively. The groups were not significantly different ($p = 0.667$) (Table 5). There were no significant differences within either group in REU score between baseline and 4 weeks at the $p < 0.05$ significance level; however, at the $p < 0.10$ significance level, there was a statistically significant difference in REU score between baseline and 4 weeks for the treatment group ($p = 0.099$) (Figure 10). At 8 weeks, the REU score was 11.17 ± 4.64 and 16.38 ± 10.04 in the treatment and control groups, respectively. The groups were not significantly different ($p = 0.234$) (Table 5). There were no significant differences within either group in REU score between baseline and 8 weeks (Figure 10).

Table 5. REU Score Data for Baseline, 4 Weeks, and 8 Weeks

REU	Baseline	4 Weeks	8 Weeks
Treatment	14.63 ± 10.77	11.38 ± 4.89	11.17 ± 4.64
Control	13.15 ± 7.20	13.88 ± 6.92	16.38 ± 10.04
P-Value	0.947	0.509	0.234

Probability of group difference provided (Mann-Whitney U test)

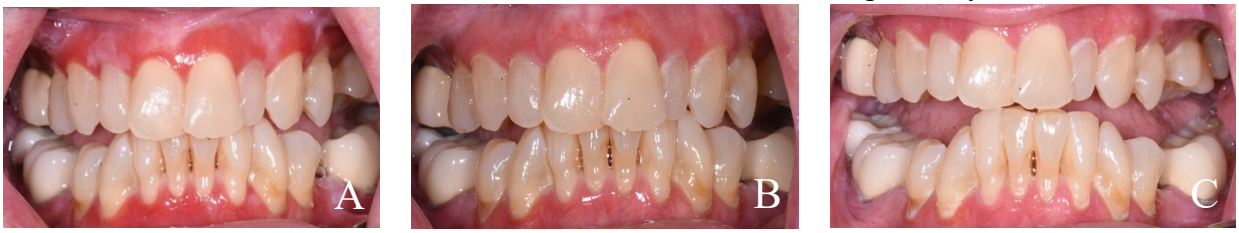
Figure 10. Clinical Severity (REU score)



*Wilcoxon Signed Ranks Test ; $p < 0.10$

Figure 11 shows example photographs for a patient at baseline, 4 weeks, and 8 weeks with REU scores listed.

Figure 11. Patient in Treatment Group at (A) Baseline, (B) 4 weeks, & (C) 8 weeks. REU scores were 45.25, 22.25, and 17.75 at baseline, 4 weeks, and 8 weeks, respectively.



Patient Satisfaction

Table 6 shows patient satisfaction in the treatment and control groups for different categories, rated on a Likert scale with 1 being very unsatisfied and 5 being very satisfied. There was a statistically significant difference between groups in "the time it took to feel relief" and "the confidence in your breath now compared to your confidence in your breath at the start of the study." For "time for relief," those in the treatment group reported a mean score of 3.91 ± 0.83,

whereas those in the placebo group reported a mean score of 3.10 ± 0.74 (p = 0.043). For "confidence in breath," those in the treatment group reported a mean score of 3.55 ± 0.93, whereas those in the placebo group reported a mean score of 2.70 ± 0.38 (p = 0.023).

Table 6. Patient Satisfaction

Satisfaction	Time for Relief	Confidence in Breath	Ability to Eat	Brushing Teeth	Mouth Looks	Mouth Feels
Treatment	3.91 ± 0.83	3.55 ± 0.93	3.18 ± 1.08	3.45 ± 1.04	3.64 ± 1.03	3.55 ± 1.04
Control	3.10 ± 0.74	2.70 ± 0.48	2.70 ± 0.82	3.30 ± 0.82	2.90 ± 0.74	2.90 ± 0.74
P-value	**0.043***	**0.023***	0.221	0.604	0.098	0.13

*Mann-Whitney U test

DISCUSSION

To the best of our knowledge, this is the first randomized, double-blind, and placebo-controlled study ever reported attempting to assess efficacy of an antioxidant gel (PerioSciences®) versus a placebo in the topical treatment of oral lichen planus. Oral lichen planus management is problematic and often aimed at palliative care rather than a cure. While many agents have been studied and prescribed, the most common method of treatment currently is topical corticosteroids.[42] However, there is a low level of confidence that topical corticosteroids are more effective than a placebo[33] and side effects are associated with the use of topical steroids[56], thus it is necessary to continue research to assess the most efficacious treatment for the disease. Due to the oxidative stress reactions found in oral lichen planus, current findings suggest that an antioxidant gel also containing essential oils may provide satisfactory relief for oral lichen planus symptoms.

In the present study, the treatment group demonstrated decreased discomfort compared to the control (placebo) group. This is evidenced by a statistically significant difference in VAS between baseline and 4 weeks and between baseline and 8 weeks in the treatment group, compared to a statistically insignificant difference in the placebo group. Results suggest the treatment group has an effective change on VAS outcomes at 4 weeks with an effect size of 0.63, indicating a large effect size according to Cohen's classification of effect sizes. This is also evidenced by a statistically significant difference in the mean VAS score between the antioxidant gel group and the placebo group at 8 weeks. The reduced discomfort during treatment may have been due to decreased inflammatory mediators, such as TNF-α, which is secreted by T-cells.[21] Decreased TNF-α levels may lead to decreased keratinocyte apoptosis, which has been attributed

to the clinical changes seen in the erosive form of oral lichen planus,[23] a presentation known to cause severe discomfort to patients.

The baseline Oral Health Impact Profile data provides interesting information on the impact of oral lichen planus on a patient's life. All patients except for one (95.5%) reported painful aching and it being uncomfortable to eat certain foods, with all patients reporting some impact of oral lichen planus on physical pain. This study further elucidates the psychological impact of oral lichen planus, as 95.5% reported psychological discomfort at baseline, with 21/22 (95.5%) of participants reported being self-conscious and 19/22 (86.4%) feeling tense because of oral lichen planus. In addition, 100% of participants reported "psychological disability," meaning they found it difficult to relax or fall asleep or have been awakened or embarrassed because of oral lichen planus. The baseline findings of this study are consistent with previous studies that have found significantly higher stress, anxiety, and depression levels in patients with the disease.[41]

No significant improvements were noted in oral health measures for patients at 4 weeks; however, at 8 weeks, patients in the treatment group reported significant improvement over the placebo group in the subscale items of "trouble pronouncing words" ($p = 0.046$) and "painful aching" ($p = 0.025$). A statistically significant improvement in "painful aching" in the antioxidant gel group versus the placebo group aligns well with the VAS data analyzed for these patients as well, as discomfort on VAS decreased in the antioxidant gel group but not in the placebo group.

More categories of significant improvements may have been noted if a different profile was used to measure oral health impact. A modified version of OHIP-14 proposed by Dugas et al. (2002) was used, in which patients simply reported whether they improved, worsened, or

stayed the same in each measure at 4 weeks and 8 weeks. If patients instead were asked to re-score each of the measures using the same Likert scale that was used at baseline, greater significant differences may have been noted.

Clinical efficacy of the treatment was measured using Piboonniyom's 2005 REU scoring system. Between baseline and 4 weeks and between baseline and 8 weeks, there were no statistically significant differences within groups at the different time points at the $p < 0.05$ significance level; however, at the $p < 0.10$ significance level, there was a significant difference in REU score between baseline and 4 weeks in the treatment group. No significant differences were found between groups at baseline and 4 weeks or between baseline and 8 weeks. While score differences might not have been significant, REU scores increased (indicating increase in clinical severity) in 60% of patients in the placebo group, but decreased in 75% of patients in the treatment group, indicating a lessened clinical severity from baseline to 4 weeks.

A potential reason for the lack of significant differences calculated despite the clear clinical change in severity evidenced in photographs (Figure 11) is due to the clinical severity scoring system that was used. The REU system has different scores for different sizes of lesions, with the cutoff thresholds being <1 cm^2, >1 cm^2 to ≤ 3 cm^2, and >3 cm^2. These thresholds are quite large, so a 2.9 cm^2 lesion would be given the same score as a 1.1 cm^2 lesion; thus, the scoring system may not account for all clinical changes that occurred. In addition, similar studies have found a similar lack of clinical improvement in patients using other treatments for oral lichen planus. In 2018, Arduino and others found that oral lichen planus patients using 0.05% clobetasol reported significant symptom improvement over a placebo group after 2 months of therapy, but that there was not a statistically significant difference in clinical severity between the two groups after two months.[43]

No participants reported any adverse effects over the course of the study period. The current first-line therapy, topical corticosteroids, often has the side effect of oral candidosis.[55] Another reported mild hyperglycemia as a side effect of prolonged topical corticosteroid.[103] The antioxidant gel did not result in oral candidosis. In fact, a patient that initially presented with candida at his initial visit had no evidence of candida at his subsequent visits, without the use of any antifungal medications.

The following limitations should be taken into account when considering the present study. Because of the relatively small sample size, further studies with larger groups of patients and controls are needed to assess the reproducibility of these preliminary results. In addition, there might not have been enough power to detect such a small effect for oral health impact or clinical severity score. Further efforts are needed to determine the effect of individual components of the gel (antioxidants versus essential oils). In this study, it cannot be determined whether the treatment effect is due to the antioxidants, the essential oils, or a combination of both. Finally, future studies are necessary in order to directly compare currently accepted treatment modalities for oral lichen planus, including topical corticosteroids.

Findings within the current literature indicate that patients with oral lichen planus have higher levels of depression, anxiety, and stress. While the present study did not show that the antioxidant gel significantly reduced psychological discomfort or disability, within the limits of this study, the antioxidant gel was statistically significant from placebo in reducing discomfort recorded using VAS and marginally reduced clinical severity recorded using an REU scoring system.

CONCLUSIONS

Within the limits of this study, it was shown that a topical antioxidant-essential oil gel is an effective means of reducing discomfort in oral lichen planus patients, and it may potentially reduce clinical severity as well. It had little impact on improvement of oral health impact profile. Despite the study limits, the treatment gel may be considered in patients with oral lichen planus who are no longer benefiting from conventional therapy with topical corticosteroids.

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