A COMPARATIVE EVALUATION OF THE EFFICACY BETWEEN TOPICAL APPLICATIONS OF PROPOLIS AND TACROLIMUS IN THE MANAGEMENT OF SYMPTOMATIC ORAL LICHEN PLANUS PATIENTS

DISSERTATION
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In partial fulfilment of the requirement for the degree of

MASTER OF DENTAL SURGERY

In

ORAL MEDICINE AND RADIOLOGY

By

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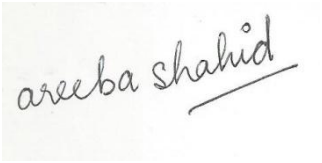

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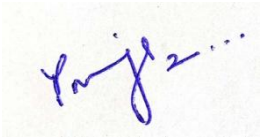

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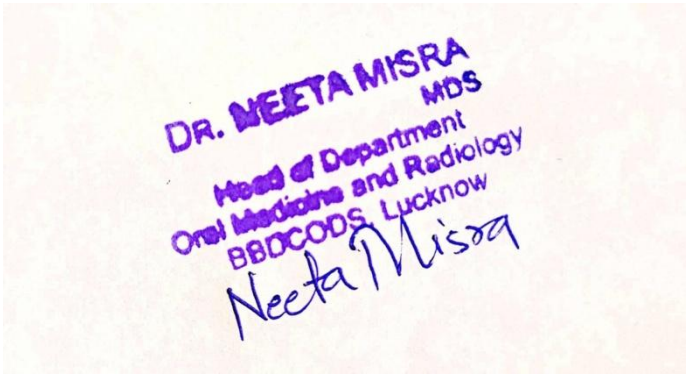

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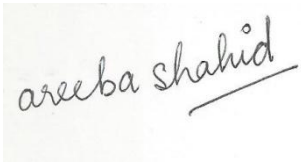

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- DR. AREEBA SHAHID

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LIST OF ABBREVIATIONS

- BBDCODS - Babu Banarasi Das College of Dental Sciences
- BBDU - Babu Banarasi Das University
- OMR - Oral Medicine and Radiology
- LP - Lichen planus
- OLP - Oral lichen planus
- CD - Cluster of differentiation
- RANTES - Regulated upon activation, normal T-cell expressed and secreted
- TGF - Transforming growth factor
- MMPs - Matrix metalloproteinases
- HSP - Heat shock protein
- HLA - Human leukocyte antigen
- NSAIDs - Non-steroidal anti-inflammatory drugs
- ACE - Angiotensin-converting enzyme
- HSV - Herpes simplex virus
- HPV - Human papillomavirus
- EBV - Epstein Barr virus
- HCV - Hepatitis C virus
- HHV - Human herpesvirus
- HIV - Human immunodeficiency virus
- OSCC - Oral squamous cell carcinomas
- TIMP - Tissue inhibitor of metalloproteinase
- TNF - Tumor necrosis factor

- CIC - Cirulating immune complexes
- C3 - Complement component 3
- OPP - Oral postinflammatory pigmentation
- OLL - Oral lichen lesion
- VAS - Visual analog scale
- NRS - Numeric rating scale
- CSS - Change in Symptoms Scale
- MOMI - Modified Oral Mucositis Index
- LDRs - Lichenoid drug reactions
- LE - Lupus erythematosdsgus
- EM - Erythema multiforme
- CUS - Chronic ulcerative stomatitis
- H&E - Hematoxylin and eosin
- PMN - Polymorphonuclear
- DIF - Direct Immunofluorescence
- BMZ - Basement membrane zone
- SSS - Salt-split skin
- ELISA - Enzyme linked immunosorbent assay
- IIF - Indirect Immunoflorescence
- DFA - Direct fluorescent antibody
- BP - Bullous pemphigoid
- Dsg - Desmoglein
- WHO - World Health Organization
- RNA - Ribonucleic acid
- HuIFNβ - Human fibroblast interferon β

- PUVA - Psoralen + Ultraviolet A
- LLLT - Low level laser therapy
- AV - Aloe-vera
- LOH - Loss of heterozygosity
- DNA - Deoxyribonucleic acid
- AD - After death
- CAPE - Caffeic acid phenyl ester
- CA - Caffeic acid
- IL - Interleukin
- HPA - Hypothalmic-Pituitary-Adrenal
- RAU - Recurrent aphthous ulcer
- RAS - Recurrent aphthous stomatitis
- VRS - Verbal Rating Scale

ABSTRACT

Introduction: Lichen planus (LP) is a chronic inflammatory, autoimmune, mucocutaneous disorder of unspecified etiopathogenesis. Corticosteroids are the first line of medications, but owing to their adverse effects, alternative therapeutic approaches such as immunomodulators (eg., Tacrolimus) and natural products (eg. Propolis) are being used and tested in the management of OLP.

Aim: This study aims to compare and evaluate the efficacy of 5% topical Propolis and 0.1% topical Tacrolimus gels in management of OLP**.**

Materials and Methods: The research groups (Group A and Group B) consisted of 20 patients (10 patients each) with clinically diagnosed symptomatic OLP. Group A received topical Propolis gel (5%) while the patients in Group B received topical tacrolimus gel (0.1%). Both the groups were evaluated at baseline visit, during active phase (7th, 14th, 21st, 28th day) , and follow-up phase (for 3 consecutive months) using visual analogue scale (VAS) and modified oral mucositis index (MOMI).

Results: The patients in both the groups showed a statistically significant reduction ($p<0.001$) in burning sensation and erythema scores from baseline till follow-up. However, tacrolimus showed a slightly better response compared to Propolis. No significant difference was noted between the groups for ulceration scores ($p=0.331$). The recurrence of the lesions was found to be non significant however, tacrolimus demonstrated a slightly higher recurrence.

Statistical Analysis : Student t-test, ANOVA and repeated ANOVA were utilised to draw results statistically.

Conclusion: The topical propolis (5%) gel was found to be of equally effective as tacrolimus (0.1%) gel in the management of OLP.

Keywords: Efficacy, Management, Oral Lichen Planus, Propolis, Tacrolimus

INTRODUCTION

Lichen planus (LP) is a common chronic mucocutaneous inflammatory disorder.[1] In Greek, "lichen" means tree moss, and in Latin, "planus" means flat. It was termed and described by a British physician *Erasmus Wilson* in 1869.[2] He considered it identical to "*lichen ruber*," formerly reported by Hebra [3]. He characterized the disease as "an eruption of pimples remarkable for their color, their figure, their structure, their habits of isolated and aggregated development." [4] Kaposi, in 1892, described the first clinical form of the disease, "*lichen ruber pemphigoid*." In 1895, Wickham noted the characteristic reticulate white lines on the surface of papules; today acknowledged as "*Wickham striae*." Histopathological changes associated with LP were first formally described by Darier.[5]

Lesions majorly occur on both oral and cutaneous surfaces (40%) together, followed by cutaneous alone (35%) and oral mucosa alone (25%).[1] Cutaneous lesion can manifest in the genital, nasal mucosa, nails, larynx, esophagus, and rarely conjunctiva. Similarly, it can also involve hair follicles resulting in scarring alopecia, termed as *Lichen planopilaris*.[6] The skin lesions are purple, polygonal, pruritic papules or plaque [5], with fine scaling on the surface and are usually self-limiting, lasting only one year or less. However, spontaneous remission of cutaneous LP after one year occurs in approximately 70% of cases.

Unconstrained remission of Oral Lichen Planus (OLP) is less likely. The reticular variant of OLP has the best prognosis because the majority of the cases are asymptomatic and undergo spontaneous remission. The persistence of OLP ranges from 5 years to up to 15-20 years in cases of ulcerative variants. It manifests in both genders, usually between the ages of 30 and 70 years. Children and adolescents are rarely affected.[1,7] It tends to affect women more than men (Carrozzo and Gandolfo, 1999; Al-Hashimi *et al*, 2007; Baccaglini *et al*, 2013). The Indian subcontinent has an exceptionally high incidence of disease, affecting 2.6% of the Indian population.[5]

OLP etiopathogenesis is complex and multifactorial, mediated mainly by T-cells (autoimmune). Factors like cytokines (Chen *et al*., 2007; Rhodus *et al*., 2007; Lavanya *et al*., 2011), adhesion molecules (Norris, 1990), and apoptosis-related molecules (Sklavounou-Andrikopoulou *et al*., 2004; Hamdy *et al*., 2016) are analogous to it. These factors have been found to exhibit overexpression in tissues and oral fluids of patients with OLP (Carmeliet, 2003; Sklavounou-Andrikopoulou *et al*., 2004; Chen *et al*., 2007; Metwaly *et al*., 2014; Hamdy *et al*., 2016). This disease is an immunological process triggered by an antigen that alters the oral keratinocytes of the basal layer, making them susceptible to cell-mediated immunity. It induces the activation of (Cluster of differentiation) CD4+T and CD8+T cells. The role of T-cell RANTES (regulated upon activation, normal T-cell

expressed and secreted) and the mast cell degranulation, leading to the release of tumor necrosis factors and interleukins, may prognosticate the chronicity of the disease process in few cases. Transforming growth factor-β1 (TGF-β1) is a cytokine that regulates many cellular processes, including cell proliferation, differentiation, apoptosis, angiogenesis, and tumorigenesis, by controlling the expression and activity of matrix metalloproteinase (MMPs) via tissue inhibitor synthesis. [8] MMPs can digest extracellular matrix and basement membrane components and damage the epithelial basement membrane indirectly.[9] Various factors like virus, trauma, stress, irritants from tobacco, heat shock protein (HSP) antigen expression can trigger OLP. New OLP lesions can develop on previously unaffected skin secondary to trauma (Koebner phenomenon) [10] and exacerbate by mechanical factors including biting/chewing habits, friction against malpositioned or ill-fitting dental prosthesis, etc. Systemic conditions like diabetes and hypertension can be associated, forming a classical triad known as "*Grinspan Syndrome*".[1,2,5,7]

According to Andreason criteria, OLP lesions vary in appearance from keratotic (reticular or plaque-like) to erosive (atrophic/erythematous), papular, ulcerative, and bullous. The lesions most commonly present as asymptomatic white linear, annular, or retiform arrangement forming typical lacy, reticular patches, rings, or striae,[5] with a uniform bilateral distribution, occurring predominantly on the buccal mucosa (up to 90%). Like cutaneous lesions, a tiny white elevated dot is present at the intersection (central lesion) of these radiating lines known as *Striae of Wickham.* [11] Other sites include gingiva and tongue with infrequent ones palate, lips, and floor of the mouth.[1,2]

The definitive diagnosis of OLP is confirmed by the histopathologic features of degeneration of basal cells and infiltration of inflammatory cells into the subepithelial layer of connective tissue. [12]

For oral mucosal lesions, topical drug application is preferred because it eliminates the requirement for ingestion and the systemic drug dissemination, yielding a more targeted delivery.[13] OLP being an immunologic condition, treatment with topical immunomodulators is appropriate. Topical steroids are widely used as primary treatment but have unfavorable side effects. Tacrolimus, a calcineurin inhibitor immunosuppressor, is reportedly effective and can be offered as an alternative, safe, secure, well-tolerated, and non-irritating therapy.[1] With minimal side effects, the use of tacrolimus could be suggested as the first line of treatment in steroid-recalcitrant lesions in patients prone to oral candidal infections and other associated immunosuppressive-adverse effects.[13,14]

Novel remedial methods are being worked upon like "*Apitherapy*," described as an art and science of treatment and wholistic healing through the honey bee and its by-products. The most important 'chemical weapon,' "Propolis," has been used as a remedy since ancient times. Propolis is a sticky, resinous substance that is collected by bees from plants and mixed with secreted beeswax, and characterized as an anti-bacterial, antifungal, antiviral, immunomodulatory, anti-inflammatory, anti-

oxidant, and anti-tumoral agent.[15,16] It has been used in folk medicine for thousands of years and is also known as Russian penicillin. [17] Propolis has found dental application in the treatment of Aphthous ulcers, Candidiasis, Pulpal, and Periodontal manifestations. [15,16] Its therapeutic properties and almost negligible side effects promise great scope in different dental applications.

Analyzing and exploring the therapeutic benefits of those mentioned above, this study is designed to evaluate the efficacy of topical Propolis and topical tacrolimus in OLP management.

AIMS & OBJECTIVES

AIM

- This study aims to compare and evaluate the efficacy of 5% topical Propolis and 0.1% topical Tacrolimus gels in management of OLP.

OBJECTIVES

- To evaluate the potency of topical Propolis in OLP patients (Group A)
- To evaluate the potency of topical Tacrolimus in OLP patients (Group B)
- To do a comparative evaluation of both the topical applications in order to assess the one with better efficacy in the management of OLP.
- To check for any recurrences in both the groups.

3.1 LICHEN PLANUS

3.1.1 INTRODUCTION

Lichen planus (LP) is a mucocutaneous disorder that mainly affects the stratified squamous epithelium of the skin and appendages.[18] It is a chronic inflammatory systemic disease of established immune-mediated pathogenesis, predominantly type IV hypersensitivity reaction.[19] British Dermatologist Erasmus Wilson coined and utilized the term 'lichen planus.' He named it after a similar presentation of the tree mosses growing on the rocks. LP occurs predominantly in the older age group, mostly among females in comparison to males. Its occurrence is rare in children and juveniles. LP occurring before puberty, mainly in infancy, has some peculiarities concerning gender, localization, clinical aspects, race, and family history. Childhood familial lichen planus is usually a disseminated type of LP having a prolonged course with relapses. Essential factors in the development of juvenile OLP include: (1) previous hepatitis B vaccination [20] ; (2) liver disease, including chronic active hepatitis [21]; and (3) genetic predisposition, such as in familial LP. [18] The cutaneous lesions of lichen planus have been classically described by 4Ps- purple, pruritic, polygonal papules. [4] It manifests on cutaneous surfaces including skin, flexor surfaces of the extremities, scalp, nails, and genitals (vulval and vaginal mucosa & glans penis). Other extraoral sites may include thighs, lower back, trunk, and neck. Mucosal lesions in the esophagus, conjunctiva, urinary bladder, nasal cavity, larynx, gut, and anus have been described. [12, 22-23]

It manifests most commonly on the buccal mucosa and tongue in the oral cavity, followed by the gingiva and alveolar ridge. [2,9,18] Rarely involved sites include the palate or vermilion border of the lip. [24] The lesions are characterized by white straie, erythema, erosions, or blisters. There are six recognized oral presentations of lichen planus: (1) reticular, (2) papular, (3) plaque, (4) atrophic, (5) ulcerative (erosive), and (6) bullous form.[1,25]

Topical steroid application has been considered to be an effective first line of treatment. However, many alternatives are available.[13] Lichen planus may resolve spontaneously within one to two years, although recurrences are common.

3.1.2 HISTORY BACKGROUND [5,26]

- **Ferdinand Ritter von Hebra (1816-1880)**, renowned dermatologist and co-founder of the renowned Vienna School of Dermatology, has attributed the first scientific description of the

skin disease, terming it "*lichen ruber planus*," in 1860. He used the term “lichen” to denote skin lesions (better known as Keratosis pilaris).[5]

- This pathologic pre-malignant condition was first described by the famed British dermatologist & physician **Sir Erasmus Wilson (1809-1884)** in 1869. He used the term '*lichen planus*' in his publication in 1869, after noting the disorder in a group of 50 patients. It obtained its name owing to the lacy white lines that hold up a close resemblance to the symbiont lichen; a composite organism consists of a fungus (the mycobiont) and a photosynthetic partner (the photobiont or phycobiont, usually, green algae) living together in a symbiotic relationship, seen growing on the rocks. Among the numerous Wilson cases, he noticed the lesions predominantly on the buccal mucosa, tongue, and pharynx. [27]
- **Heinrich Köbner (1838–1904)** described the ‘*Kobner phenomenon*' in 1872. In 1876, he published a paper describing his original patient exhibiting the development of isomorphic pathologic lesions in response to trauma on previously uninvolved sites of patients with skin diseases. Most commonly seen in patients with psoriasis, but also observed in eczema and lichen planus. [10]
- The oral lesions in lichen planus were further noted and described by **Unna** and **Crocker** in 1882, [28], the latter noting white lesions and spots on the buccal mucosa and symmetric plaques on lateral borders of the tongue in several cases.
- **Thibierge**, in 1885 [29] first described the oral lesions systematically. He observed that the lesions occurred on the buccal mucosa and tongue in most cases, with specific differences in appearance, and described them in considerable detail.
- In 1892, **Kaposi** [30] reported “*lichen ruber pemphigoides”* as the first vesiculobullous variant of this disease.
- It was **Audry** in 1894 [31] who pointed out that oral lesions could occur in the absence of skin lesions. Till then, oral lesions were considered merely an accompaniment to the generalized skin eruptions.
- In 1895, **Louis Frédéric Wickham** [11] (1861-1913) was first acknowledged for describing this characteristic, fine, white, or grey lines, also known as *Wickham’s striae*. In Latin, striae stand for grooves or dots that are appreciated on the top of the pruritic papular rash of lichen planus of the skin and are also seen with OLP.
- **Poor** [32] , in 1905 gave the first description of vesiculobullous lesions occurring on the oral mucosa as "the formation of cavities in the mucosa, corresponding in character to subepithelial bullae and characterized by exudation from surrounding blood vessels."

- **Dubreuilh** [33] , in 1906 stated that involvement of oral mucous membrane alone was more common than involvement of the skin without mucosal lesions. He felt that histologically oral lesions were comparable in all points to skin lesions, and due to ease of oral biopsy, he suggested it as a diagnostic aid.
- **Lieberthal**, in 1907 first described the oral manifestations of the lichen planus in the American literature and characterized the differences between the lesions of the tongue and buccal mucosa.
- **Darier**, in 1909 was credited for the first documentation of the histopathological changes associated with lichen planus. [5]
- In 1910 **François Henri Hallopeau** reported the first case of OLP-related oral carcinoma.
- **Milian and Fouquet** [34] reported oral ulcerative lesions in 1929, and atrophic LP of the tongue too was described by Lortat–Jacob *et al.* in the same year.

3.1.3 EPIDEMIOLOGY

a) PREVALENCE

In the literature, different prevalence figures for OLP have been reported. It affects 0.5–2% of the population, with notable variation by geography and diagnostic criteria.[5, 35] Literature reports a prevalence of 0.5% in a sorted Japanese population, 1.9% in the Swedish population, and 2.6% in the Indian population. These figures may represent an underestimation because minor lesions may easily be overlooked.[1,2]

Hellier FF [36] **(1940)** reported the prevalence of LP to be 0.1 to 1.25 % in dermatological outpatients.

Pindborg LL, Chawla TN, Misra RK *et al.* [37] **(1965)** conducted a study for 121 consecutive days, in which 10,000 patients were examined in the admission clinic at the Dental College, King George's Medical College in Lucknow, Uttar Pradesh, India. Similar studies were conducted in Bombayites [38] and Gangalore, South India. [39] They noted the frequency of white oral lesions such as oral carcinoma, leukoplakia, leukokeratosis, leukoedema, submucous fibrosis, and lichen planus in these three different Indian urban populations and reported a prevalence of 0.02-0.22% in, each consisting of 10,000 patients.

Pindborg JJ, Mehta FS, Daftary DK, *et al.* [40] **(1972)** conducted a house to house survey among 7,369 villagers in Ernakulum district of Kerala, India. They were examined for oral lichen planus besides the prevalence of other pre-malignant conditions. The OLP lesions were mainly confined to the buccal mucosa, and a considerably higher prevalence rate of 1.5 % was observed. Tobacco consumption habits were also associated and noted to be highly prevalent among these patients.

Mohan RPS, Ghanta S, Verma S *et al.* [41] **(2013)** conducted a retrospective study to evaluate the influence of meteorological factors on the incidence of LP in clinically diagnosed patients during the three successive years: 2008, 2009, and 2010, in Moradabad district (Western Uttar Pradesh, India). The highest number of patients (735) were recorded in summer and the lowest (56) in winter. The summer peak was attributable to the intensity of sun exposure.

From the data, we see that through various prevalence rates that various studies have reported, they all seemed to fall in a similar range with very slight variations among the various populations studied during different times.

b) AGE

OLP is commonly said to affect the middle-aged population commonly, but numerous cases have been reported in children and the elderly. The onset of the disease occurs most commonly in the middle age group people, with a mean age of 50 years. [1-2,5,22] Erasmus Wilson, in 1869 described his study patients as being in their 40's and 50's.

In adults:

Bhonsle RB, Pindborg JJ, Gupta PC, *et al.* [42] **(1979)** carried out a house-to-house survey, comprising of 10,000 South Indian villagers, and found that the age-adjusted incidence rate per 1,000 persons for OLP was found to be 2.1 for males and 2.5 for females, based upon a 10-year follow-up study. The most significant incidence was in the age group 55-64 for males and 45-54 for females.

Xue JL, Fan MW, Wang SZ *et al.* [43] **(2005)** conducted a study on a total of 674 patients with histologically confirmed OLP. In their study, the mean age at presentation was 49 years for women and 52 years for men, with a broad age range of 10–78 years.

Munde AD, Karle RR, Wankhede PK, *et al.* [44] **(2013)** carried out a retrospective study to examine the epidemiological and clinical characteristics of 128 OLP patients in India's rural population. In their findings, the mean age at presentation was 35.5 years for males, 39.1 years for females. The mean age was 36.9 years at diagnosis, and the peak of age frequency distribution was observed in the third decade (35.2%) of life.

Chitturi RT, Sindhuja P, Parameswar RA *et al.* [45] **(2015)** conducted a study comprising of 58 patients in the age range of 11-70 years. The mean age of the patients included was 5.72 ± 13.10. The maximum numbers of patients were in the age group 41–50 years age group (34%), followed by 31–40 years (21%), 61–70 years (14%), 21–30 years (14%), 51–60 years (12%) and 11–20 years (2%) age groups.

The available literature to date highlights the disease of the middle-aged population, usually affecting males a decade earlier than females.

In children:

LP occurrence is rare in children. However, it has even been described in an infant under six months, [22] with the youngest case documented in a child aged three months by Pusey WA. [46] Pediatric patients comprise only 2% to 3% of all patients. [47]

Childhood familial lichen planus occurred at an early age and with greater severity. **Mahood JM** [48] **(1983)** examined nine members of four families, each of whom suffered from LP. He found that 12% of his familial LP patients manifested the disease before age 10.

Singal A [49] **(2005)** documented a case of familial OLP in a family of 3 successive generations: a woman (65 years), her son, and grandson with no cutaneous lesions.

It has been recognized that childhood LP is more common in the tropics, and the more prone to this condition are the children of Asian origin. There is a higher prevalence in the Indian population suggesting potential differences in the genetic background and/or environmental triggers.

Alam and Hamburger [50] **(2001)** documented six cases of OLP in Asian male patients between the ages of 6–11 years, without any relevant medical or family history.

Handa and Sahoo [51] **(2002)** conducted a study to analyze the clinical profile of childhood LP prevailing in north India. 87 patients with LP were examined during 12.5 years (July 1988 to December 2000) of observation. The age of onset was between 8 months and 12 years (mean, 7.1 years). Involvement of the palms and soles and upper eyelids were the unusual features observed besides the classic presentation.

Laeijendecker R, Van Joost T, Tank B [52] **(2005)** reported OLP in three children, an Asian girl aged 11 years, an Asian boy aged 16 years, and a caucasian girl aged 14 years. They indicated that OLP in childhood is rare but seems to occur preferentially in the Asian race, with clinical features resembling OLP in adults.

A paucity of reported cases of juvenile OLP may be due to lack of patient and parent awareness of lesions, lack of recognition by practitioners, low incidence of autoimmune diseases, and precipitating factors such as stress. [53]

c) GENDER

In the literature, different prevalence figures for OLP are available and vary from 0.5% to 2.2% as reported, with a notable female predominance.[2,25,54-55]

Scully and El-Kom [22] **(1985)** in their comprehensive review, stated that "LP affects both the genders, although occasional surveys have suggested a male predominance, the vast majority, from several different countries, have revealed that some 60 to 65% of patients are females".

According to **Boyd and Nelder** [12] **(1991)**, "among patients with OLP, 63 to 67 % are women, and between 55 to 65 % of patients with cutaneous LP are women".

Silvermann, Gorsky, Lozada-Nur *et al.* [56] **(1991)** conducted two prospective studies of 570 cases and 214 cases in a similar population in 1985 and 1991, revealing a female predominance with 67% and 71 % of subjects and overall 69% subjects in 784 cases being females.

Varghese SS, George GB, Sarojini SB *et al.* [57] **(2016)** conducted a retrospective study in Southern India population which 122 patients of OLP showed prevalence in females than males.

Few exceptional studies reveal a male predominance or equal sex distribution in OLP patients.

Anjum R, Singh J, Kuduva S [58] **(2012)** conducted a cross-sectional study comprising 33 cases of clinically diagnosed OLP. They found that males and females are almost equally affected; 16 males were affected against 17 females, and M:F ratio was 1:1.1.

In the retrospective study by **Munde AD, Karle RR, Wankhede PK *et al.*** [44] **(2013)** among 128 OLP patients in India's rural population, their findings revealed M:F ratio to be 1.61:1.

Sachdev R, Mukerjee S, Garg K *et al.* [59] **(2019)** conducted a study on a total of 102 clinical and histopathological diagnosed OLP patients, in which males (75.4%) were predominantly present.

3.1.4 ETIOPATHOGENESIS

a) ETIOLOGY

Though the exact etiology of this disease is still unknown, OLP etiopathogenesis is intricate and apparently depends on the interaction of discrete factors [2] , which are as follows: [5]

- **Genetic background**: Familial cases are sporadic. Scientists (**Watanabe T *et al*., 1986; Porter SR *et al*., 1997; McCartan BE *et al*., 1997 and Ognjenovic M *et al*., 1998**) [60-63] in their studies have mentioned an association with Human leukocyte antigen (HLA) -A3, A5, A11, A26, A28, B3, B5, B7, B8, B16, B27, B51, Bw35, Bw57, DR1, DR2, DR3, DR9, DRw9, DQw1 observed in both cutaneous and oral forms.
- **Dental materials:** Many restorative materials used intraorally have been identified as triggering elements for OLP. **Scully C *et al.*** [6,18] (1998, 2008) and **Issa Y *et al.*** [64] (2004) in their reviews have stated the role of metals such as silver amalgam, cobalt, gold, chromium, palladium, and non-metals such as composite. Prolonged use of denture wear can also precipitate the disease, as reported by **Rath and Arnav (2016)** [65] in their case.
- **Drugs/Medications:** The first association of drugs with LP-like lesions presenting as lichenoid reactions were noted when quinacrine and mepacrine were used as antimalarials during World War II (**Schmitt *et al*., 1945; Savage, 1958**).[18] Systemic drugs may trigger oral

lichenoid drug reactions, including non-steroidal anti-inflammatory drugs (NSAIDs), beta-blockers, sulfonylureas, angiotensin-converting enzyme (ACE) inhibitors, antimalarials, and contact allergens including toothpaste flavorings, especially cinnamates, as reported by **Scully C *et al.* [18] (1998) and Serrano-Sánchez P [66] (2010)** in their reviews.

- **Infectious agents**: It has been suggested that OLP has been related to bacteria such as the spirochetes and Gram-negative anaerobic bacillus, but this has not been confirmed yet.[18] (**Vainio E *et al*., 2000 and Ashktorab H *et al*., 2007**) [67-68] in their studies revealed the role of Helicobacter pylori (HP) as an etiological agent. However, no significant association between the two was established (**Zenouz AT *et al*., 2010 and Hulimavu SR *et al*., 2014**).[69-70] **Ertugrul AS *et al.*** [71], 2013 found an association of few periodontopathogenic microorganisms (*Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythia, and Treponema denticola*) with the patients of OLP. Culture studies have demonstrated Candida species in the mouths of 37 to 50% of OLP cases (**Simon and Hornstein, 1980; Lundstrom *et al*., 1984**) and also demonstrated in biopsies in between 0 and 17% of cases with no apparent predilection for any clinical type of OLP (**Holmstrup and Dabelsteen, 1974; Lundstrbm *et al*., 1984; Hatchuel *et al*. 1990).[18] However, Mehdipour M *et al.* [72] (2010)** found an insignificant association between candida infection and OLP. Association with various viral agents such as Herpes simplex virus (HSV), Human papillomavirus (HPV), Epstein Barr virus (EBV), Hepatitis C virus (HCV), Human herpesvirus 6 (HHV-6), and Human immunodeficiency virus (HIV) has been reported by (**Kumari R *et al*., 2009; Yildirim B *et al*., 2011; Patil S *et al*., 2012 and Alaizari NA *et al*., 2016**).[73-76] In OLP, HCV replication has been reported in the epithelial cells of mucosal lesions. HCV-specific T lymphocytes in the pathogenesis of OLP may play a role.
- **Autoimmunity: Scully C *et al.*** [6] (1998) and **Abbate G *et al.*** [77] (2016) have mentioned the occasional association of OLP with systemic/autoimmune disorders such as "primary biliary cirrhosis, chronic active hepatitis, myasthenia gravis, thymoma, etc."
- **Bowel disease**: OLP is infrequently described in relation to bowel diseases such as "coeliac disease, ulcerative colitis, and Crohn's disease ", as mentioned by **Georgakopoulou EA *et al.*** [78] (2012) their review.
- **Food allergies***:* A minority of OLP patients have been reactive to certain foods (**Eisen,** 1993) and food additives such as cinnamonaldehyde (**Maibach, 1986; Allen and Blozis, 1988**).[18] **Wray *et al.*** [79] (2000) in their study of 1252 participants found hypersensitivity to food additives (benzoic acid), perfumes, and flavorings (cinnamonaldehyde).

- **Stress:** Field has termed the skin as the "shock organ" for emotional stress, manifesting in the form of numerous skin diseases. Clinical observations have recognized psychological stress as either precipitating, aggravating, or prolonging many skin diseases and the psychosomatic aspects of many disorders. Altman and Perry, 1961 reported that, of 197 patients with LP, "10% were aware of a triggering stressful incident at the onset of their LP". Other studies by **Chaudhary S [80] (2004); EL. Tawil, Sediki, Hassan [81] (2009) and Kalkur, Sattur, Guttal [82] (2015)** report the role of psychological stress as an etiological agent of OLP. It has been proposed that prolonged emotional stress causes psychosomatization, which in turn may contribute to the initiation and clinical expression of OLP. Psychosocial and emotional stress can also possibly precipitate reticular OLP to transform to the erosive form. [82] But there is still controversy concerning the role of stress as a significant or minor etiologic factor in the pathogenicity of LP.
- **Habits:** The role of smoking as an etiological factor in some Indian communities has been insinuated. (**Pindborg *et al.*** [33] ,1972) . Studies by **Mansur and Kılıç** [83] (2004); and **Gönül M *et al.*** [84] (2015) also reported the link between the two. Betel nut chewing is also prevalent in Indian patients with OLP than in those without (**Pindborg *et al.*, 1972** and **Trivedy CR *et al.*, 2002**) [33, 85].
- **Trauma:** Trauma has not been positively cited as an etiological agent in LP, though its underlying mechanism may allow other etiological factors to exert their effects. [18]
- **Diabetes and hypertension***:* Impaired glucose metabolism is observed in a high percentage of OLP patients. **Bagewadi and Bhoweer** [86] (2011) conducted a study including 150 subjects divided into three groups, showing only four diabetic patients and eight hypertensive patients among 50 OLP patients. They concluded that diabetes mellitus and hypertension do not play a direct role in the etiology of lichen planus. However, a meta-analysis study by **Mozaffari HR, Sharifi R, Sadeghi M** [87] (2016) showed an association between OLP with DM. A triad of Diabetes mellitus, hypertension, and OLP is called Grinspan syndrome.[7,12] Phadnis *et al.* [88] (2018) presented a case report of a 48 year old female patient with a significant clinical triad of Grinspan's syndrome. **Gowhar O, Ain TS, Sultan S** [89] (2019) conducted a study including 1000 diabetic patients, out of which 12 (1.2%) had OLP, and 11 patients belonged to type II diabetes mellitus. Only one patient was diagnosed with having OLP suffering from Type I diabetes. Out of those 12 patients, four patients had high blood pressure suggesting Grinspan's syndrome (33.3%).
- **Miscellaneous associations:** OLP has infrequently been associated with other systemic conditions such as psoriasis (**Delaney *et al.*, 1993**), lichen sclerosis (**Marren *et al.*, 1994**),

urolithiasis (**Halevy and Feuerman, 1983**), glomerulonephritis (**Cottoni *et al*., 1988**), Turner's syndrome with endocrinopathies (**Kurgansky and Burnett, 1994**), etc.[18]

b) IMMUNOPATHOGENESIS

Schifter M, Fernando SL, Li J [23] **(2013)** and **Gupta S, Jawanda MK** [5] **(2015)** in their comprehensive reviews have discussed in detail the various mechanisms hypothesized to be associated with the immunopathogenesis, are as follows:

1. Antigen-specific cell-mediated immune response
2. Loss of tolerance evidenced by the development of autoantibodies against self-antigens and the promotion of autoimmunity
3. Role of the humoral immune response
4. Non-specific immune mechanisms
5. Genetic factors.

1. Antigen-specific cell-mediated immune response

The LP antigen is unknown, although the antigen may be a self-peptide, thus defining LP as an actual autoimmune disease. An early event in LP lesion advancement may be keratinocyte antigen expression or unveiling at the future lesion site stimulated by systemic drugs (lichenoid drug reaction), contact allergens in dental restorative materials or toothpaste (contact hypersensitivity reaction), mechanical trauma (Koebner phenomenon), bacterial or viral infection, or an unidentified agent. Heat shock proteins (HSP) are upregulated in OLP and considered as potential antigens. The native chaperones HSP70 is proposed to be integral in the disease onset and progression **(Tyagi, Shetty, and Urs** [90] **, 2012)** However, alternatively, their overexpression may be a common decisive pathway that links a variety of exogenous agents (systemic drugs, contact allergens, mechanical trauma, bacterial or viral infection) in the pathogenesis of OLP. Vulnerability to OLP may result from dysregulated HSP gene expression by distressed oral keratinocytes or self-HSP recognition, which is more likely due to decreased immune response.

Sugerman, Savage, Xu *et al.* [91] **(1995)** conducted a study to assess the potential role of HSP in the pathogenesis of OLP. They derived sections from the normal oral mucosa, ulcerated site, and dysplastic OLP site; and assessed HSP expression using immunohistochemistry. They concluded that diverse exogenous agents might cause upregulated expression of HSP by oral mucosal keratinocytes, and a different reaction of cytotoxic T lymphocytes may further result in tissue destruction, a characteristic of OLP lesions.

Scully C *et al.* [6] **(2008)** stated in their review that cell-mediated immunity appears to play a substantial role in the pathogenesis of OLP. The majority of T cells adjacent to damaged basal keratinocytes are CD8+ T cells. The specific immune response to this unidentified antigen involves the following steps:

- Migration of T lymphocytes into the epithelium;
- Activation of the T-lymphocytes;
- Killing of keratinocytes

2.Non-specific mechanisms in OLP

Some of the T cells in the OLP lymphocytic infiltrate are unspecific. The mechanisms involved aim at the movement of lymphocytes into the epithelium to destroy the keratinocytes. The various factors proposed to be responsible for non-specific immune responses are:

1. The epithelial basement membrane
2. Matrix metalloproteinases
3. Chemokines
4. Mast cells

- **The epithelial basement membrane**

Scully *et al.* [6] **(2008)** and **Roopashree MR *et al.*** [92] **(2010)** in their reviews stated that keratinocytes maintain the structure of the epithelial basement membrane by secreting collagen IV and laminin V into it, ensuring survival. Keratinocyte apoptosis triggered by intra-epithelial CD8+ cytotoxic T cells may cause epithelial basement membrane disruption in OLP, which allows migration of the non-specific T lymphocytes into the subepithelial zone.

- **Matrix metalloproteinases (MMPs)**

MMPs, with at least 20 members, is a family of zinc-containing endo-proteinases. The principal function of MMPs is the proteolytic degradation of connective tissue matrix proteins **(Vu and Werb** [93] **, 2000).**

Sutinen M, Kainulainen T, Hurskainen T, *et al.* [94] **(1998)** studied the expression and distribution of MMP-1 and -2, their tissue inhibitors in oral squamous cell carcinomas (OSCC), lymph node metastases, OLP, oral epithelial dysplasias, and normal buccal mucosa using in situ hybridization, immunohistochemistry, and zymography. They verified that the MMP-1 expression, besides being

weak, was restricted to fibroblasts of the sub-epithelial region, while MMP-2 was not detected in the ten samples studied.

Rubaci AH *et al.* [95] **(2012)** studied the expression of MMP-2 and MMP-7 in the epithelium, and found that connective tissues from OLP lesions were more significant than normal oral mucosa.

According to **Payeras MR *et al.*** [96] **(2013)**, the culture supernatants derived from the OLP lesional T cells express a higher concentration of MMP-9 activators than OLP or healthy control peripheral blood T cells. MMP-9 activators released from the T cell help in activating pro-MMP nine resulting in basement membrane disruption.

In contrast to **Sutinen *et al.*** [94] **(1998); Agarwal N, Carnelio S, Rodrigues G** [97] **(2019)** evaluated the presence and possible role of MMP-2 and tissue inhibitor of metalloproteinase (TIMP-2) in OLP etiopathogenesis and also as an indicator of malignant transformation, in 30 histopathologically confirmed cases. They observed clear expression of MMP‑2 and TIMP‑2 in all the cases as mediators in the pathogenesis of OLP.

- **Chemokines**

Chemokines are pro-inflammatory cytokines. **Zhao ZZ *et al.*** [98] **(2001)** in their study; while **Sugerman and Savage** [9] **(2002)** and **Payeras MR *et al.*** [96] **(2013)** in their reviews have discussed the role of RANTES (regulated on activation, normal T cell expressed and secreted). It is a chemokine family member produced by various cells, including activated T-lymphocytes, bronchial epithelial cells, rheumatoid synovial fibroblasts, oral keratinocytes, and mast cells. RANTES secreted by OLP lesional T cells may attract mast cells into the developing OLP lesion and subsequently stimulate mast cell degranulation. Degranulating mast cells in OLP would release tumor necrosis factor (TNF-α) and chymase, upregulating OLP lesional T cell RANTES secretion. Such a cyclical mechanism may underlie OLP chronicity.

- **Mast cells**

In OLP, the mast cell degranulation liberates a range of pro-inflammatory mediators such as TNF-α, chymase, and tryptase. **Sharma R *et al.*** [99] **(2011)** ,in their study, found that approximately 60% of mast cells were degranulated in OLP, compared with 20% in the normal buccal mucosa. Thus mast cells have been suggested to be involved in the OLP pathogenesis.

3.Autoimmune response

OLP is postulated to be an autoimmune disease. **Lavanya N *et al.*** [55] **(2011)** and **Schifter M, Fernando SL, Li J** [25] **(2013)** in their reviews have discussed the role of autoimmunity in OLP disease pathogenesis. It is supported by many autoimmune features, including disease chronicity,

adult-onset, female predilection, association with other autoimmune diseases, depressed immune suppressor activity in OLP patients, and the presence of autocytotoxic T cell clones in LP lesions.

Four hypotheses have been proposed implicating autoimmune reaction in OLP, they are:

1. Inadequate antigen-specific immunosuppression in OLP – lack of transforming growth factor (TGF-b1).
2. Malfunctioning of immune privilege in OLP.
3. Keratinocyte apoptosis and Langerhans cell maturation in OLP.
4. Heat shock proteins

4. Humoral immunity

Lukac J *et al.* [100] **(2006)**, in their study, identified circulating antibodies, including autoantibodies against desmogleins 1 and 3 in the sera of 25 patients with an erosive form of oral lichen planus. This presence indicates a role of humoral immunity in oral lichen planus.

Popovska M *et al.* [101] **(2014)** conducted a study among 19 patients with erosive OLP to examine the role of Immunoglobulin (Ig) A, circulating immune complexes (CIC), and component C3 as indicators of a humoral immune response. Changes in the parameter values correlated with changes in oral mucosa, thereby emphasizing their role in the pathogenesis of OLP.

A cross-sectional study comprising 100 LP patients by **Rambhia KD *et al.*** [102] **(2018)** provides the serological concentrations of various antibodies from western India. It was found that 65% patients showed the presence of at least one of the six autoantibodies studied, while 35% tested negative for all six of them. The significant presence of autoantibodies suggested the possible role of humoral immunity in the patients.

Identifying antibodies linked to lichen planus may help in identifying appropriate diagnostic tests and therapeutic targets. Well-controlled studies with a larger sample size are the need of the hour to confirm the role of humoral immunity in lichen planus.

3.1.5 CLINICAL FEATURES [103]

a) CUTANEOUS LESIONS

LP is a mucocutaneous disease that affects the skin and appendages. The prevalence of cutaneous LP in the general population is from 0.9 to 1.2% **(Boyd and Neldner [12] , 1991)**. Cutaneous LP generally occurs in individuals between the ages of 25 and 60 years, with no gender or racial predilection as reported by **Scully C *et al.*** [18] **,1998.** The cutaneous lesions of LP are characterized by 6 Ps: purple,

polygonal, pruritic, papules and plaque. [104] The cardinal symptom of LP is severe pruritis, which varies and usually resolves within one to two years **(Weston and Payette [105], 2015)**. Hyperpigmentation may be sequelae that are often marked but temporary. Initially, LP has been evident as a cutaneous and mucosal eruption, though rarely it can manifest with only oral or nail findings. LP usually begins as discrete, flat-topped papules 3 to 15 mm in diameter, which may coalesce into larger plaques. They appear red early in the disease, but soon they take on a reddish-purple or violaceous hue (**Gorouhi F, Davari P and Fazel N [23] , 2014)**. The center of the papule may well be slightly umbilicated, and its surface is covered by characteristic, outstanding grayish white lines, called Wickham striae (**Rivers JK, Jackson R, Orizaga M [106] (1986); Steffen C, Dupree ML, Louis-Frédéric [11] (2004)**. The face frequently remains uninvolved. The lesions are located on the flexor surfaces of limbs, internal facet of knees and thighs, trunk and may emerge on the trauma lines, displaying the Köbner phenomenon, although it can occur anywhere on the skin surface. [4,18,23] Some patients report involvement of the genitals [107] with features similar to dermatological lesions, scalp (lichen planopilaris), and nail beds (**Scully C *et al.* [18], 1998)**. Infrequently, there is laryngeal, esophageal, and conjunctival involvement (**Rennie CE *et al.* [108] , 2011)** and **Gorouhi F, Davari P and Fazel N [23] ,2014). Kumara, Rangaraj, and Karthikeyan [109], 2016** reported an interesting case of *drawstring dermatitis*, which marked an initial presentation of LP in a 54-year-old female patient.

Literature describing children with lichen planus demonstrate as having cutaneous manifestations majorly with a low incidence of oral involvement. **Handa and Sahoo [51] (2002)** in their study, out of 87 patients with LP, the involvement of skin alone was observed in 75 (86.2%) children and mucosa alone only in one (1.1%) child. Besides the classic presentation, involvement of the palms and soles and upper eyelids was observed.

b) ORAL MANIFESTATIONS

In the literature, different prevalence figures for OLP have been reported and vary from 0.5% to 2.2% (**Edwards and Kelsch [110] , 2002 ; Eisen D [111] , 2003)**. In the oral cavity, the disease presumes a somewhat different clinical appearance than on the skin. It is marked by lesions that consist of radiating white, velvety, gray, annular, thread-like papules in a linear, and retiform arrangement forming typical lacy, reticular patches, rings, and streaks. [2, 6, 9] A tiny white elevated dot is present at the intersection of white lines known here as striae of Wickham compared to Wickham striae in the skin.[106] The lesions are asymptomatic, with a symmetrical distribution, occurring anywhere in the oral cavity, and may appear weeks or months prior to the appearance of cutaneous lesions. However, unilateral distribution can also occur, as reported by **Bajpai M *et al.* [112] , 2014**. The posterior buccal

mucosa (about 90%) is the most frequent site of involvement, followed by the tongue (about 30%), alveolar ridge/gingiva (about 13%), labial mucosa. Occasionally on the lips alone (Itin *et al*., 1995; Allan and Buxton, 1996). Lesions on the palate, vermilion border of the lip, floor of the mouth, and upper lip are uncommonly noted (Axell and Rundquist, 1987). [18,23-24,35,56] As reported by **Scully C *et al.*** [22] **, 1985** approximately 10% of patients with OLP lesions are confined to the gingiva. Gingival lichen planus presents as small, raised white, lacy papules or plaques. Erythematous lesions affecting the gingiva result in desquamative gingivitis, also seen in various other autoimmune disorders.

Classification: The clinical evaluation of the OLP lesions rests on six clinical forms, described by **Andreasen** [113] **(1968)** as follows,

A) Reticular

B) Atrophic

C) Erosive

D) Plaque-like

E) Papular

F) Bullous

A) Reticular: Characterised by thin, slightly raised, white lines that connect in a pattern resembling lacework or reticular, annular appearance. The arcuate pattern of white lines, referred to as Wickham striae, can be present on erythematous or non-erythematous mucosa. Usually asymptomatic and commonly noticed by a dental health professional. The most common site for this pattern is the buccal mucosa (85%). Lesions may be localized to the interdental line area or involve the entire buccal mucosa, extending into the vestibule and retromolar area. Other sites include the lateral border of the tongue and attached gingiva (Shklar G and McCarthy P [114] ,1961). A common feature is a bilateral distribution (Andreasen, 1968; Holmstrup *et al*., 1988; Silverman *et al.*, 1991). Reticular OLP may eventually progress to the severe subtype, such as the erosive form. [1,18,64]

Munde AD, Karle RR, Wankhede PK, *et al.* [44] **(2013)** carried out a retrospective study to examine the epidemiological and clinical characteristics of 128 OLP patients in India's rural population. In their findings, buccal mucosa was the most common site (88.20%), and reticular type was the most common pattern (83.5%), followed by erosive (15.6%) and atrophic OLP (0.78%).

Chitturi RT, Sindhuja P, Parameswar RA *et al.* [45] **(2015)** conducted a study comprising 58 patients from 11-70 years. The most common form of OLP seen was the reticular subtype, and buccal mucosa was the most commonly affected site, with > 60% of patients had post-inflammatory hyperpigmentation.

B) Atrophic: This symptomatic form of LP accounts for 5 to 44%. Pain, burning sensation, or discomfort has been recorded in 43 to 91% of the patients included in larger cohorts of OLP patients

(Scully C *et al.* [18] ,1998) . It presents as a diffuse, red or erythroplakic lesion with fine white striae evident at the margins of the atrophic zones. The common site is the attached gingiva which manifests as desquamative gingivitis and, apart from these, have also seen to manifest in the marginal gingival and alveolar mucosa with lingual gingival less commonly involved. May involve dorsum of the tongue, causing atrophic glossitis. [1-2,35,114]

Munde AD, Karle RR, Wankhede PK, *et al.* [44] (2013) in their findings, reported atrophic form to be of least prevalence (0.78%) in 128 patients.

Keshari D, Patil K, Mahima VG [115] (2015) reported 16 (59.26%) of the total 27 patients presented with the atrophic form of OLP while 11 patients (40.74%) with the erosive form.

C) Erosive: OLP patients with ulcerative/erosive lesions accounts for 9 to 46% **(Scully C *et al.* [18] ,1998)**. It is a symptomatic variant related to trauma influences or local irritation. It usually appears as irregularly shaped ulcerated areas with a whitish-yellow pseudomembrane, present on intensely erythematous mucosal areas. The degree of atrophy, ulceration and erythema may vary from lesion to lesion. Junction of the red and normal mucosa shows faint, white, radiating striae. Some patients exhibit desquamative gingivitis too. It may represent mucous membrane pemphigoid or pemphigus vulgaris, making histopathologic evaluation essential. Typically, it has a multifocal pattern of distribution. [1,23]

Munde AD, Karle RR, Wankhede PK *et al.* [44] (2013) among their 128 OLP patients found erosive form to be the second most prevalent variant (15.6%).

Tak and Chalkoo [116] (2015) evaluated 50 patients with OLP for demographic trends, clinical profiling, and relevance to thyroid disorders. They found an erosive pattern to be the second most prevalent variant in 11 patients out of all.

D) Plaque-like: The plaque-form is seen in about 23% of patients **(Eisen D [117] , 2002)**. It is slightly elevated and smooth to a slightly irregular form and may be multifocal, although the dorsum of the tongue and buccal mucosa are primary sites. **Mollaoglu N [118] (2000)** reported that plaque-like lesions resemble leukoplakia and occur as homogenous white patches, so they must be histologically ruled out. This form is substantially more common among tobacco smokers. (Thorn *et al.*, 1988) reported that plaque-type lesions developed in patients who initially had atrophic and/or ulcerative lesions. Plaque-like oral lichen planus resolves in only 7% of cases.

E)Papular: This variant is characterized by small asymptomatic spaced out white pinpoint papules that portray a “pebbled white or gray appearance" and can be easily missed. It is referred to as the initial and transient phase of OLP, making it a rare diagnosis. [23]

F)Bullous: Bullous oral lichen planus is a rare variant that appears as small bullae or vesicles varying from a few millimeters to several centimeters in diameter that tend to rupture easily. On

rupturing, they leave an ulcerated, painful surface. The bullous form is most commonly seen on the tongue (lateral borders or ventral surface) [114], followed by buccal mucosa, particularly in the posteroinferior areas adjacent to the second and third molar teeth lateral margins tongue. The lesions are seldom seen on the gingiva or inner aspect of the lips.[1]

Patil A *et al.* [119] **(2012)** reported a 34 year old female patient with a chief complaint of burning sensation in the oral cavity accomapanied with generalized pruritis, scalp, and cutaneous lesions diagnosed as bullous LP.

Considering mucosal prevalence in children, **Scully, de Almeida, Welbury** [120] **(1994)** reported three females with OLP, 10–11 years old, with no relevant underlying medical or family histories. **Sharma and Maheshwari** [121] **(1999)** reported 15 out of 50 cases (30%) with mucosal lichen planus involvement.

c) PIGMENTATION

Another clinical sign associated with OLP is 'hyperpigmentation.' Oral postinflammatory pigmentation (OPP) is a discoloration of the oral mucosa associated with chronic inflammatory disorders such as OLP, Oral lichen lesion (OLL), and alike lesions. It is characterized by an excess of melanin production and deposition within the basal epithelial layer and connective tissue of mucosal areas affected by chronic inflammation **(Murti PR *et al.*** [122] **, 1979)**. Factors like race, smoking, stress and anxiety, Addison's disease, and post-inflammatory changes causing melanin incontinence have been associated with OLP.

Chitturi RT, Sindhuja P, Parameswar RA *et al.* [45] **(2015)** conducted a study comprising 58 patients from 11-70 years. More than 60% of patients had hyperpigmentation associated with the site affected by OLP. They found a significant relationship between the reticular pattern (follows a more chronic course and results in inflammatory changes of the oral mucosa.) and the older age group (51–70 years) with hyperpigmentation. Hyperpigmentation was due to postinflammatory changes and repeated occurrence and healing of OLP.

3.1.6 DIAGNOSIS

a) CLINICAL DIAGNOSIS

Taking a good history and clinical presentation of the lesions is sufficient to make a provisional diagnosis of OLP. The presence of classic skin lesions facilitates even a better diagnosis. Wickham's striae present extraorally and/or intraorally makes the diagnosis readily discernible. Various

measurement scales such as visual analog scale (VAS), numeric rating scale (NRS), etc., can be used to assess the pain/burning sensation or discomfort levels and clinical symptoms in OLP patients.

Chainani W *et al.* [123] **(2008)** conducted a study on 33 patients to validate the NRS, VAS, and Change in Symptoms Scale (CSS) in evaluating symptoms of OLP and the Modified Oral Mucositis Index (MOMI) in measuring the indications of OLP. The patients had their signs and symptoms assessed by each of these scales at four different time points throughout their participation in a randomized, controlled clinical trial of Curcuminoids over a 7-week follow-up period. Mild to high correlations were found between VAS, NRS, and CSS. The correlation of NRS was more substantial than that of VAS with clinical signs. Considerable changes from baseline at each follow-up in all the scores were seen.

b) DIFFERENTIAL DIAGNOSIS [6,121,124-125]

The differential diagnosis of OLP varies by lesion morphology. It must be differentiated from oral lichenoid lesions, frictional keratosis, leukoplakia, lichen sclerosus, pemphigus, lupus erythematosus, erythematous candidiasis, mucus membrane pemphigoid, and chronic ulcerative stomatitis **(Scully and El-Kom, 1985; MacLeod and Soames, 1991; Church and Schlosser, 1992; Lavanya N *et al.*, 2011; Chiang CP *et al.*, 2018)** [18,55,126] disorders that particularly may clinically and histologically resemble OLP, and malignancy must be excluded.

The diagnosis of reticular LP can solely be based on the clinical findings. Interlacing white striae which appear bilaterally on the posterior buccal mucosa is often characteristic of the particular disease. Difficulties often arise when there is superimposed candidal infection, masqueradeing the classic reticular pattern and eventually elicits the erosive/atrophic forms of OLP.

Lichenoid drug reactions (LDRs) are usually unilateral in distribution **(Sehgal VN** [127]**, 2011)**, accompanied by a history of a drug intake such as oral hypoglycaemic agents, ACE inhibitors, and NSAIDs. The most reliable method to diagnose LDRs is to note if the reaction resolved after the offending drug is withdrawn and returned if the patient is rechallenged. Dental restorative material-induced lichenoid reactions can be identified when OLP-like lesions are constricted to the areas of the oral mucosa in proximity to restorative materials, usually amalgam. A positive patch test, a robust clinical correlation of proximity of restoration, and biopsy suggestive of diffuse lymphocytic infiltrate instead of a subepithelial band advocate a diagnosis of oral lichenoid reactions. Solitary plaque-like lesions of leukoplakia are most challenging to differentiate from plaque-like OLP. The fact that leukoplakia affects more men than women, with a strong association of tobacco habit consumption, may hint at the nature of the lesion. A biopsy can usually be used to reconfirm the

diagnosis, especially when multiple areas of leukoplakic involvement may give a similar appearance.[124]

Clinically, lupus erythematosus (LE) lesions most often resemble erosive OLP but tend to be less symmetrically dispersed. The keratotic striae of LE show characteristic radiation from the central focus, much more delicate and subtle than Wickham's striae, and the Biopsy of LE shows a characteristic perivascular infiltrate **(Lavanya N *et al.* [55] , 2011).** Erosive or atrophic types that usually affect the gingiva should be differentiated from mucous membrane pemphigoid and pemphigus vegetans, as both present with desquamative gingivitis. Both the lesions occur as solitary erythematous lesions, unassociated with white striae. Peeling of the epithelium from the epithelial-connective tissue junction on application of slight lateral pressure in the unaffected area (Nikolsky's sign) helps differentiate. A biopsy can diagnose pemphigus or pemphigoid from the perilesional tissue, which shows subepithelial or intraepithelial fragment histologically. In some cases, erythema multiforme (EM) can mimic bullous lichen planus, but EM is generally acute in nature and usually involves the labial mucosa. [124]

Chronic ulcerative stomatitis (CUS), affecting the oral mucosa, also clinically and histologically resembles OLP. Diagnosis of CUS is based on direct immunofluorescent studies (DIF) studies. In this the autoantibodies are directed against p63 in the epthelial basal and parabasal layers. These lesions can be differentiated from OLP as CUS does not respond well to the corticosteroid therapy. [125]

Schlosser BJ [28] **(2010)** has enumerated few other significant lesions that should be differentiated:

Aphthous ulcers :

- Non-keratinized mucosal of the lip, buccal, ventral tongue, floor of the mouth
- Single or multiple discrete oval ulcers
- Erythematous halo, yellow pseudomembrane
- Rarely herpetiform (10–100 1–2 mm ulcers clustered)
- Hematoxylin and eosin (H&E): necrosis, ulceration, Polymorphonuclear (PMN) dust
- Direct Immunofluorescence (DIF): negative

Dermatitis herpetiformis

- Oral lesions common
- Subtle, diffuse erythema and superficial ulcerations
- Tooth enamel defects (pits) common
- H&E: neutrophilic mucositis
- DIF: granular IgA at Basement membrane zone (BMZ)

Epidermolysis bullosa acquisita

- Traumatic oral ulcers and bullae
- Desquamative gingivitis
- H&E: pauciinflammatory subepithelial bulla
- DIF: linear IgG at BMZ
- Salt-split skin (SSS): linear IgG at base of the blister
- Enzyme-linked immunosorbent assay (ELISA): autoantibodies to type VII collagen

Familial benign pemphigus (Hailey–Hailey disease)

- Rare ulcers, painful vegetative papules
- H&E: intraepithelial acantholysis, no dyskeratosis
- DIF: negative
- Indirect Immunofluorescence (IIF): negative

Graft versus host disease

- Diffuse erythema and mucositis (both keratinized and non-keratinized mucosa)
- White reticular plaques and erosions
- Loss of filiform papillae
- Loss of gingival stippling
- H&E: basalar vacuolar degeneration, subepithelial lymphocytic infiltrate

Primary herpes simplex stomatitis

- Erosive gingivostomatitis
- Small, punched-out ulcers that may coalesce to large ulcers with scalloped borders.
- Recurrent on the gingiva, hard palate, and dorsal tongue
- Positive Tzanck, Direct fluorescent antibody (DFA), viral culture, serology for HSV 1 and 2
- H&E: intraepidermal bulla with neutrophils, keratinocyte necrosis, multinucleated giant cells, positive
- Immunohistochemistry for HSV 1 or 2

Recurrent herpes simplex stomatitis

- Small, punched-out ulcers that may coalesce to large ulcers with scalloped borders.
- Recurrent on the gingiva, hard palate, and dorsal tongue

Linear IgA bullous dermatosis

- Oral lesions common (up to 70%)

- Large ulcers on tongue, palate, buccal mucosa
- Desquamative gingivitis
- DIF: linear IgA at BMZ, less often also IgG, Complement component (C3)
- IIF: linear IgA at BMZ
- SSS: linear IgA at the roof of the blister

Paraneoplastic pemphigus

- Predominant labial mucosa and vermilion involvement
- Underlying malignancy
- H&E: suprabasalar acantholysis, interface/lichenoid mucositis
- DIF: intercellular IgG, C3 with or without BMZ deposition of IgG, C3
- IIF: intercellular staining of the transitional epithelium (rat bladder)
- ELISA: autoantibodies to Bullous pemphigoid (BP) 180, BP230; Desmoglein (dsg) 1, dsg3
- Immunoprecipitation: antiplakin autoantibodies

c) HISTOPATHOLOGICAL DIAGNOSIS

Given the fact that other mucocutaneous diseases, including pemphigus, pemphigoid, lichenoid reactions, pre-malignant dysplastic lesions, and contact allergy, are included in the differential diagnosis of LP [2], a biopsy must be performed to confirm a diagnosis **(Muller S [128] , 2017)**

Dubreuill first explained the histopathology of OLP in 1906, and it was revised by **Shklar** [129] in 1972, who gave three characteristic features:

- overlying keratinization;
- liquefaction degeneration of the basal cell layer;
- a dense subepithelial band of lymphocytes

Kramer, Lucas, Pindborg, *et al.* [130] **(1978)** have highlighted the "1978 World Health Organization (WHO) diagnostic criteria", supported by the following three findings:

1. Usually, the keratinized layers exhibit either hyperparakeratosis or hyperorthokeratosis, often with a thickening of the granular cell layer and a saw-toothed appearance of the rete pegs. The saw-toothed appearance is typical in the skin lesions but less frequent in the oral lesions. The thickness of the epithelium varies, but atrophy is often seen, and the erosive epithelium is evident in some cases.
2. An eosinophilic band may often replace liquefaction degeneration of the basal cell layer.
3. A dense, bandlike lymphocyte infiltration in the superficial part of the lamina propria and close to the epithelium is mainly composed of T cells. The presence of B cells is uncommon.

Another critical feature of OLP is the presence of Civatte (colloid) bodies containing one or more pyknotic nuclear fragments in shrunken epithelial cells in the region of the basal cell layer.

WHO diagnostic criteria (1978) for oral lichen planus [130]

Clinical criteria -

- Presence of white papule, annular, reticular, plaque-type lesions, gray-white lines radiating from the papules
- Presence of lacelike network of slightly raised gray-white lines (reticular pattern)
- The presence of atrophic lesions may also cause bullae, with or without erosion.

Histopathologic criteria-

- Presence of thickened para or orthokeratinized layer in site with usually keratinized, and if site normally non-keratinized this layer may be fragile
- Presence of Civatte bodies in the basal layer, epithelium, and superficial part of the connective tissue
- A well-defined bandlike zone of cellular infiltration is confined to the superficial part of the connective tissue.
- Signs of 'liquefaction degeneration' in the basal cell layer

The WHO criteria for histopathologic diagnosis of OLP in 1978 did not describe the difference between OLP and OLLs; hence **Eisenberg** [131] **, 2000** proposed the following essential histopathological criteria:

(a) basal cell liquefaction,

(b) bandlike lymphocytic infiltrate at the epithelial-stromal junction, with obfuscation of the basal cell region, and

(c) a regular epithelial maturation pattern. Atypical cytomorphologies, including nucleus enlargement or hyperchromasia, prevalent dyskeratosis, and increased mitotic figures, are excluded from OLP diagnostic features. A heterogeneous population of inflammatory infiltrate, a deeper submucosal extension of infiltrating beyond superficial stroma, and perivascular infiltration indicate lichenoid infiltrate rather than OLP.

Modified WHO diagnostic criteria of OLP -2003:

Proposed by **Van der Meiji and van der Waal** [132] **(2003)**

Clinical criteria-

- Presence of more or less symmetrical, bilateral lesions.
- Presence of lacelike network of slight raised grayish-white lines, i.e., reticular pattern

- Erosive, bullous, atrophic, and plaque-type lesions are identified in the presence of reticular lesions only as a subtype elsewhere in the oral mucosa.
- In all other lesions similar to OLP but do not qualify the criteria as mentioned earlier, the term used is "clinically compatible with."

Tak and Chalkoo [116] , 2015; Joshy *et al.* [133] , 2018 in their studies enrolled patients with clinically diagnosed atrophic/erosive OLP, based on modified WHO clinical criteria.

Histopathologic criteria

- Consisting mainly of lymphocytes, a well-defined bandlike zone of cellular infiltration confined to the superficial part of the connective tissue consists primarily of lymphocytes.
- Indications in the basal cell layer of liquefaction degeneration.
- Absence of epithelial dysplasia.
- The term "histopathologically compatible with" to be used when the histopathologic features are less noticeable.

Munde *et al.* [44] (2013) and Chitturi *et al.* [45] (2015) in their studies enrolled patients with OLP, based on modified WHO criteria, both clinical and histopathological.

Final diagnosis OLP or OLL

Clinical as well as histopathologic criteria should be included to achieve a final diagnosis:

- OLP - A diagnosis of OLP requires fulfillment of both clinical and histopathologic criteria
- OLL - The term OLL will be used under the following conditions:
    1. Clinically typical of OLP, histopathologically only compatible with OLP
    2. Histopathologically typical of OLP, clinically only compatible with OLP
    3. Clinically compatible with OLP, histopathologically compatible with OLP

According to **De Rossi and Ciarrocca [1] (2014)** the histopathologic features of LP have a slight variation among the different clinical types, which are as follows:

Reticular

- Orthokeratosis and parakeratosis are seen in combination with acanthosis
- Intermittent areas of epithelial atrophy
- The basement membrane is thickened, with a dense band of T lymphocytes

Erosive

Thinning and ulceration of the epithelium with complete loss of rete ridge formation

- Dense T-cell infiltrate extending well into the middle and upper levels of the epithelium.

- Liquefaction of the basement membrane and vacuolization and destruction of the basal cell is seen in most areas.
- The epithelium is often lost, showing underlying connective tissue

Plaque like

- Similar to the striae of the reticular form, without the intermittent areas of epithelial atrophy
- Orthokeratosis and parakeratosis are seen in combination with acanthosis
- The basement membrane is thickened, with a band of T lymphocytes less dense than in the reticular form

Bullous

- Subepidermal bulla showing degeneration of the epidermal basal layer
- Other features of LP

d) DIRECT IMMUNOFLUORESCENCE

The direct immunofluorescence (DIF) technique detects immunoglobulins (IgA, IgG, IgM), C3 deposition, and fibrinogen within biopsy specimens obtained from patients suffering from autoimmune pathologies, bullous diseases, and oral lichen planus. In lichen, planus DIF is usually performed in the lesional mucosa. [25]

Sano SM *et al.* [134] **(2008)** conducted a retrospective study on 136 patients with a clinical diagnosis of OLP and bullous diseases. The DIF detection rate was 65.8% in patients with OLP, with different DIF values in other lesions. They also suggested that perilesional biopsies have the same detection rate as distant biopsy sites, and punch samples exhibited a higher sensitivity rate than those taken with a scalpel. The intraoral areas most sensitive to DIF were the floor of the mouth, ventral surface of the tongue, upper labial mucosa, hard palate, and buccal mucosa. Gingiva and dorsum of the tongue were not considered ideal sites.

Buajeeb W *et al.* [135] **(2015)** conducted a study to evaluate the prevalence and pattern of DIF in a group of 82 Thai patients with OLP. Of these, 82.9% showed positive DIF. Buccal mucosa was the most sensitive site. The most typical finding was shaggy fibrinogen along the basement membrane with or without positive IgM deposition on the colloid bodies. DIF is a definitive diagnostic tool for OLP appearing as desquamative gingivitis and excluding other vesiculobullous lesions and lupus erythematosus.

3.1.7 MANAGEMENT

As OLP is a chronic disease, the patient's medical history, psychological state, possible drug interactions, and economic background must be considered when evaluating the cost-effectiveness of any treatment modality. Asymptomatic OLP lesions do not require treatment. However, the symptomatic lesions (atrophic and erosive form alone or in combination with reticular pattern) exhibit burning sensation to severe pain; causing interference with speech, eating, and swallowing does require therapy **(Carrozzo and Gandolfo [111], 1999; Eisen D [136] , 2002).** Mechanical trauma of dental procedures, friction from sharp cusps, rough dental restorations, and poorly fitting dental prostheses exacerbate symptomatic OLP factors and should receive attention. Re-assurance of the patient, maintaining good oral hygiene, and oral prophylaxis is essential and can enhance healing in desquamative gingivitis cases, observed in atrophic and erosive gingival OLP. Several treatment regimens have been designed to improve the management of symptomatic OLP, but a permanent cure is not yet possible.

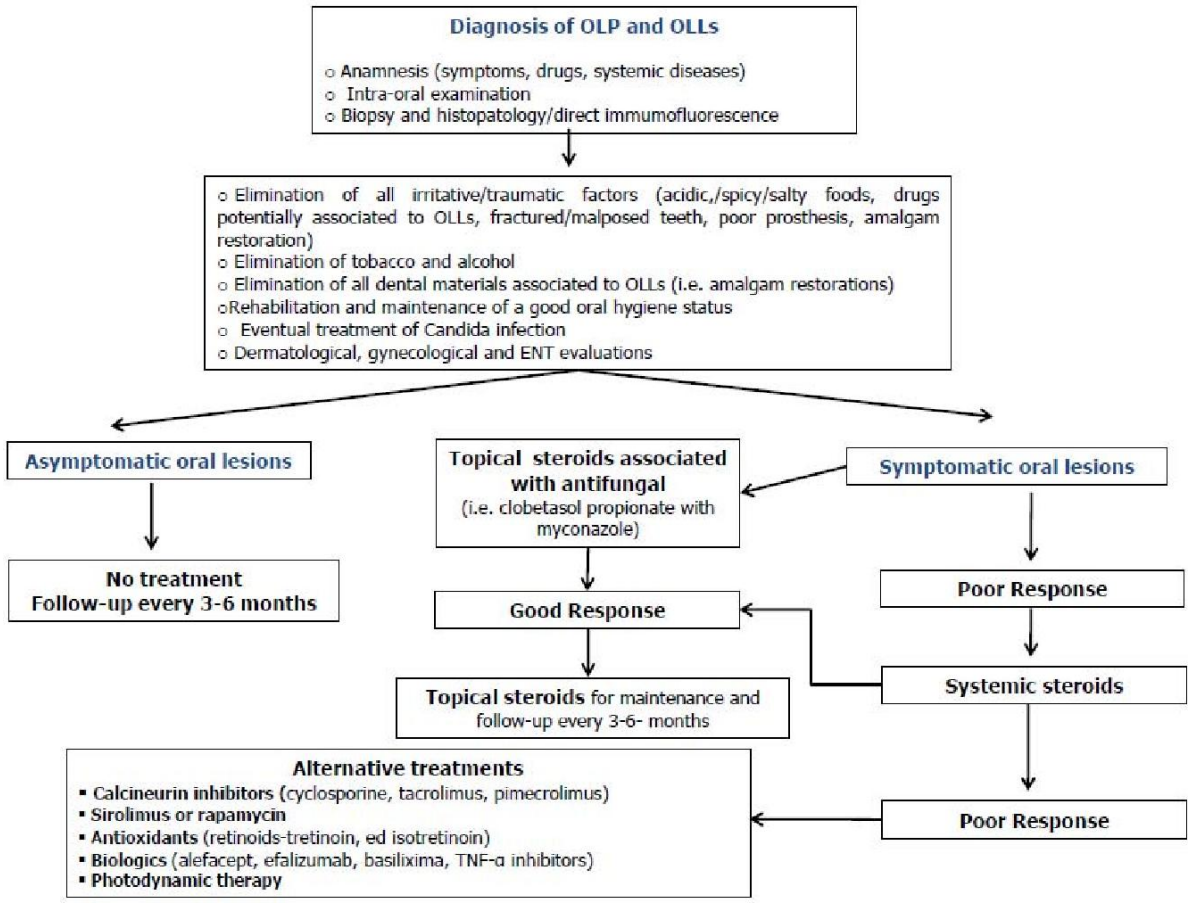


Figure 1. An algorithm discussing the management of OLP **(modified from Carrozzo M *et al.* [136] (2009)** Picture courtesy: **Bagan J, Compilato D, Paderni C, *et al.* [13] (2012)**

a) PHARMACOLOGICAL MODALITIES (Carrozzo and Gandolfo [136] ,1999; Scully, Eisen and Carrozzo [137] , 2000)

A.) Corticosteroids

Topical

- Triamcinolone acetonide
- Clobetasol propionate
- Betamethasone phosphate
- Betamethasone valerate
- Fluocinolone acetonide
- Fluocinonide
- Hydrocortisone hemisuccinate

Topical corticosteroids remain the mainstay of OLP treatment. Topical corticosteroids in adhesive paste form, comprising of betamethasone valerate, clobetasol, triamcinolone acetonide, fluocinolone acetonide and fluocinonide, have been extensively used. Other forms available include aqueous solution, mouthwashes, pellets, aerosol, etc. Triamcinolone Acetonide is commonly used either in paste or lozenge form **(Zegarelli, Kutscher, Silvers, *et al.* 1960)**. An oral suspension of triamcinolone has exhibited beneficial effects **(Zegarelli, Kutscher, and Mehrhof, 1969).** Acute pseudomembranous candidiasis is only the common side effect of topical corticosteroid therapy.

Swarna YM *et al.* [138] **(2011)** conducted a randomized comparative study, including 30 symptomatic OLP subjects, divided into groups A and B to receive topical Tacrolimus 0.03% ointment and triamcinolone acetonide 0.1% ointment application respectively, twice daily for four consecutive weeks. The burning sensation was recorded using VAS. Subjects in both groups showed a significant reduction in burning sensation; however, it was higher (98%) in group A than in group B (72%). Relapses occurred in 2 subjects in group A and 3 subjects in group B after the cessation of the respective treatments.

Systemic corticosteroids

- Prednisone
- Methylprednisolone

Systemic corticosteroids are considered to be a better alternative treatment for patients with recalcitrant erosive OLP or multisite disease, unresponsive to topical steroids.

Intralesional corticosteroids

Intralesional injections of hydrocortisone, triamcinolone acetonide, dexamethasone, and methylprednisolone have been used in OLP treatment. However, the injections are not invariably efficient, can be painful, and have a localized effect such as mucosal atrophy.[18]

B.) Immunomodulatory agents

- Azathioprine
- Cyclosporin
- Dapsone
- Enoxaprine
- Glycyrrhin
- Hydroxychloroquine sulfate
- Interferon
- Levamisole
- Mesalamine
- Tacrolimus
- Thalidomide

➢ **Calcineurin inhibitors**

Calcineurin inhibitors are immunosuppressives derived from microbes that have been fundamentally used to treat immune-mediated cutaneous disorders and transplant medicine. The principle agents include Tacrolimus, pimecrolimus, and cyclosporine. Calcineurin inhibitors cause inhibition of cytosolic calcineurin function, causing suppression of the proinflammatory cytokines generation. These inhibitors bind to distinct cytoplasmic proteins of T-lymphocytes (cyclosporine binds to cyclophilin; whereas Tacrolimus and pimecrolimus bind to FK506-binding protein) to form complexes that lead to inhibition of calcineurin causing suppression of cytokine production. Tacrolimus also inhibits histamine release and an afresh synthesis of prostaglandin D2 from the mast cells activated by IgE **(Al Johani *et al.* [139] , 2009)** Clinical efficacy in the management of few immunological oral mucosal disorders has been discussed in the literature.

Topical Tacrolimus

Tacrolimus is a potent immunosuppressive agent belonging to the macrolid family, derived from *Streptomyces tsukubaensis.* It inhibits T-cell activation at 10-100 times lower concentrations. In the treatment of symptomatic OLP, topical Tacrolimus has been reported to be effective. Desquamative gingivitis, pemphigus vulgaris of the lip, oral Crohn disease, etc. **(Al Johani *et al.* [139] , 2009)** It has been topically utilized in the form of an ointment, mucoadhesive paste (mixed with orabase), and

mouthwashes. Topical Tacrolimus, available in two concentrations i.e. 0.3% and 0.1%, is proficient in delivering pain relief, is well tolerated, and induces complete healing of OLP lesions **(Rozycki TW *et al.* [140] , 2002)** Since minimal side effects are reported, the use of Tacrolimus could be suggested as a first-line treatment in steroid-recalcitrant lesions, in susceptible patients for oral candidiasis and other immunosuppressive- adverse effects. [13] Although topical Tacrolimus is effective and well-tolerated by OLP patients, few of them have reported flare-ups soon after the treatment cessation.

Shichinohe R *et al.* [141] (2005) reported two cases with severe recalcitrant erosive OLP. In case 1, a 64-year-old man, on his entire lower lip and buccal mucosa, presented with a 5-month history of painful erosions. He experienced rapid relief from pain, and improvement was obtained within five weeks of 0.1% topical Tacrolimus treatment. Blood Tacrolimus level was kept within a safe level (2.5 ng/mL). In case 2, a 68-year-old man presented with a 2-month history of painful erosions on his right lower lip and buccal mucosa. He experienced rapid improvement of both lesions within 4 weeks of the start of Tacrolimus application. No significant irritation or recurrence was observed in both cases.

Lozada-Nur and Sroussi [142] (2006) conducted a study to evaluate the clinical efficacy and safety profile of Tacrolimus powder in Orabase 0.1% in patients with OLP (7 patients) and OLL (3 patients). All patients received a 1-week treatment of Fluconazole priorly and were provided with a 15 g container of the study medication, to be applied three times a day for two weeks. All patients experienced significant relief from the treatment, and Tacrolimus was concluded to be highly effective with a relatively safe profile.

Laeijendecker R *et al.* [143] (2006) conducted a study to compare the efficacy of topical tacrolimus with triamcinolone acetonide ointments in patients with OLP. Twenty patients in each group (group I and II) were treated with topical Tacrolimus 0.1% and triamcinolone acetonide 0.1% ointment, respectively, 4 times daily. The clinical effect was recorded after 6 weeks. In group I, 6 patients healed, 12 showed improvement, and 2 showed no improvement. In group II, 2 patients healed, 7 improved, and 11 showed no improvement. Topical tacrolimus 0.1% ointment induced a better initial therapeutic response than triamcinolone acetonide 0.1% ointment. However, relapses occurred frequently within 3–9 weeks of the cessation of treatment.

Tacrolimus could be considered superior to topical corticosteroids (triamcinolone, clobetasol, and cyclosporin) to treat OLP. It is an effective and secure alternative due to its low systemic absorption, better mucosal absorption, low incidence, and secondary effects. [14]

Study authors	Tacrolimus Dose & Regimen	Response
Hodgson *et al.* [144] (2003)	0.1% Tacrolimus in paraffin ointment twice daily	Effective
Thomson *et al.* [145] (2004)	0.1% Tacrolimus in Orabase, once or twice daily	Effective
Byrd *et al.* [146] (2004)	0.03% and/or 0.1% Tacrolimus	Effective
Laeijendecker *et al.* [143] (2006)	0.1% Topical tacrolimus ointment, 4 times daily for 6 wk	More effective than triamcinolone acetonide
Corrocher *et al.* [147] (2008)	0.1% Tacrolimus ointment, 4 times daily for 4 weeks	More effective than clobetasol
Radfar *et al.* [148] (2008)	0.1% Tacrolimus ointment (number of applications/day reduced from 4 to 1 over 6 wk)	Equally effective Tacrolimus and clobetasol

Table 1. Documentation of few randomized controlled trials and retrospective studies using topical Tacrolimus in the management of OLP.

Adverse effects of Tacrolimus

Study authors	Side effects reported in few patients	Evidence of systemic absorption
Vente *et al.* [149] (1999)	Burning sensation	Undetectable (< 1.5 ng/mL)
Rozycki *et al.* [140] (2002)	Burning sensation and sore throat	Unreported
Kaliakatsou *et al.* [150] (2002)	Tingling and burning sensation, dysgeusia, nausea, mild headache, constipation	Detectable (3-28.6 ng/mL)
Hodgson *et al.* [144] (2003)	Burning sensation, dysgeusia, and headache	Detectable (2.7-11 ng/mL); decreased during therapy
Byrd *et al.* [146] (2004)	Local irritation, burning and tingling sensation; dysgeusia	Unreported
Thomson *et al.* [145] (2004)	Paraesthesia, burning sensation, dysgeusia, and	Detectable (1.5 -2.9 ng/mL)

	nausea	
Fricain *et al*. [151] (2005)	Mucosal pigmentation	Undetectable (< 1.5 ng/mL)
Laeijendecker *et al.* [143] (2006)	Transient burning/stinging sensation	Unreported
Corrocher *et al.* [147] (2008)	Transient worsening of burning sensation for 4-5 days	Undetectable (< 1.5 ng/mL)

Table 2. Documentation of adverse effects of topical Tacrolimus reported by few authors.

However, **Shichinohe *et al.* [141] (2006)** and **Morrison *et al*. [152] (2002)** reported no adverse effects and presence of Tacrolimus in the blood in their patients.

Systemic Tacrolimus

Systemic Tacrolimus is substantially less expensive and 10 to 100 times more potent than cyclosporine.

Cyclosporin

Cyclosporin, thereby suppressing T-cell cytokine production, is a polypeptide that inhibits the transcription of several cytokine genes. It is found beneficial in the treatment of OLP, either topically or in the form of mouthrinse. In OLP patients, systemic absorption of cyclosporin is probably low, and most studies did not detect its presence in the peripheral blood. For the initial control of OLP, cyclosporin can be used. However, it should not be considered the first drug of choice because of this medication's adverse effects, including bad taste, transient burning sensation on initial application, high cost of long-term treatment, and the availability of better alternatives. Severe side effects of cyclosporin taken systemically, include hypertension and nephrotoxicity, which precludes its use in OLP. [139]

Conrotto, Carbone, and Carrozzo [153] **(2006)** conducted a randomized, comparative, double-blind study to compare the effectiveness and cost-effectiveness of clobetasol and cyclosporin in the topical management of OLP. Forty patients were divided into two groups to receive clobetasol propionate or cyclosporin (placed in 4% hydroxyethylcellulose bioadhesive gel) respectively for 2 months. Eighteen of 19 clobetasol-treated patients (95%), while 13 of 20 cyclosporin-treated patients (65%) improved after 2 months of therapy. Symptom wise 18 clobetasol-treated patients (95%) and 17 cyclosporin-treated patients (85%) improved. 33% of clobetasol-treated patients and 77% of cyclosporin-treated patients were stable two months after the end of therapy. Clobetasol produced

significantly more side effects than cyclosporin. It was concluded that clobetasol is more effective than cyclosporin in inducing clinical improvement, but the two drugs have comparable symptoms.

- **Azathioprine**

Azathioprine is used either as a corticosteroid-sparing agent or as monotherapy. Dermatologists recommend this drug for the treatment of severe recalcitrant diseases in the oral cavity. Adverse effects include bone marrow suppression, and long-term use may increase the risk of internal malignancy. [137]

Lozada F [154] **(1981)** conducted an open clinical trial to assess the synergistic effect of azathioprine with prednisone in 12 patients. The minimum efficient dose of prednisone when azathioprine was never more than 25 mg/day ranged as low as 5 mg/day. Azathioprine effectively enhanced corticosteroid activity, allowing lower doses of prednisone with satisfactory clinical efficacy and a marked reduction in side effects. However, the results were no better than systemic steroids alone or systemic steroids in combination with topical steroids.

- **Dapsone**

Dapsone is used in the treatment of erosive OLP with some benefits. It should be considered in resistant cases, mainly when severe erosive lesions are present. Significant adverse effects such as hemolysis and headache have been reported. Generally, the use of dapsone in the treatment OLP is precluded.[137]

Matthews, Pinkney and Scully [155] **(1991)** studied 15 patients suffering from recalcitrant desquamative gingivitis due to OLP or benign mucous membrane pemphigoid. They were treated with dapsone over 3 months. 58% of patients had been benefitted from the therapy. Of the 7 patients with OLP, 1 showed complete recovery, and 3 showed minor improvement. Of the 5 patients with mucous membrane pemphigoid, 3 showed some improvement, and 2 received no benefit. 3 patients withdrew from the trial due to side effects of the dapsone, such as headaches and nausea. It was concluded that dapsone therapy might be an alternative to failed conventional modalities in managing desquamative gingivitis.

- **Glycyrrhizin**

Nagao Y *et al.* [156] **(1996)** investigated the effects of glycyrrhizin in 9 OLP patients with chronic liver dysfunction and had tested positive for HCV antibody and HCV Ribonucleic acid (RNA). Glycyrrhizin was administered intravenously, at a dose of 40 ml (0.2% solution) daily, for 4 consecutive weeks. Six (66.7%) of the nine patients improved clinically, suggesting its usefulness in treating OLP.

- **Interferon**

Two small uncontrolled studies by **(Sato, Yoshida, Yanagawa *et al.* [157] , 1985; Pedersen A [158] , 1998)** suggested a topically applied gel preparation containing human fibroblast interferon (HuIFNβ) and IFNα cream may improve erosive oral lichen planus.

Despite few successes, interferon has been reported to trigger or worsen OLP lesions.

- **Levamisole**

Levamisole is used as an immunomodulator in OLP but may occasionally induce lichenoid lesions.

Lu, Chen and Eng [159] (1998) conducted an open trial on 41 patients over 3 years. They were given levamisole 150 mg/day and prednisolone 15 mg/day for 3 consecutive days each week, along with topically applied dexamethasone in orabase. The therapy showed remission of signs and symptoms within 2 to 8 weeks of treatment. All patients remained symptom-free for more than 6 months with very few adverse effects.

The combination of levamisole and Chinese medicinal herbs can achieve complete remission more than either therapy given alone **(Sun and Chiang [160] , 2001).**

- **Mesalazine**

Mesalazine (5-aminosalicylic acid) is a relatively new drug widely used to treat inflammatory bowel diseases. Interestingly, mesalazine can induce the formation of lichenoid lesions **(Alstead, Wilson and Farthing [161] , 1991)**

Demarosi F, Oltolina A, *et al.* [162] (1998) in a trial compared topically applied mesalamine (5%) with clobetasol propionate (0.05%) in 25 OLP patients. Mesalamine produced a complete absence of symptoms in 57% of patients, partial response in 21.3%, and no response in 9%, results not significantly different from those following clobetasol.

- **Thalidomide**

Thalidomide has the anti-immunologic and anti-inflammatory properties of suppressing t-cell function. It is used to treat oral disorders such as aphthous stomatitis, erythema nodosum leprosum, rheumatoid arthritis, myelodysplastic syndromes, and Crohn's disease. Systemic thalidomide is known to completely heal erosive OLP in a patient unresponsive to systemic and topical corticosteroids, psoralen + ultraviolet A (PUVA), etretinate, dapsone, and cyclosporine **(Dereure, Basset-Seguin and Guilhou [163] , 1996; Franks and Macpherson [164] , 2004).** However, it may lead to the formation of lichenoid lesions. [137]

C.) Retinoids

Topical

- Fenretinide
- Isotretinoin
- Tazarotene
- Tretinoin

Recently, a new topical retinoid, tazarotene, has been introduced to treat OLP. **Petruzzi M, De Benedittis M, Grassi R, *et al.*** [165] **(2002)** conducted a small randomized placebo-controlled study conducted in which 12 patients with hyperkeratosic OLP were treated with tazarotene gel 0.1% twice daily or with a placebo for eight consecutive weeks. A significant reduction in the lesions was observed, as compared to the control group. Transitory side-effects include burning sensation and taste abnormalities.

Petruzzi M, Lucchese A and Lajolo C [166] **(2013)** extensively reviewed 16 studies, in which 280 OLP patients were topically treated with different classes of retinoids. Isotretinoin was the most frequently employed retinoid. Isotretinoin gel 0.1% and tretinoin ointment can produce significant improvement in patients with OLP. Only transient burning sensations or irritation on the initial application have been reported. Moreover, following treatment with topical tretinoin, histologic examination demonstrated that keratinization might decrease significantly or disappear. Topical fenretinide has proved beneficial in OLP treatment with minimal side effects but is not readily available.

Systemic

- Acitretin
- Etretinate
- Isotretinoin
- Temarotene
- Tretinoin

Hersle K, Mobacken H and Sloberg K [1667] **(1982)** conducted a study using a mean dose of 0.98 mg/kg/day of etretinate for two months, 93% of treated patients had a complete or partial response, but all developed adverse effects (cheilitis, conjunctivitis, skin and mouth dryness, hair loss, pruritus, headache), which required discontinuation of the drug in 26% of patients.

Because of possible side-effects of systemic retinoids and low remission rates, the primary use of retinoids is dissuaded. Both systemic and topical retinoids should be used as adjuvant therapy only.

D) Antifungals

Candida albicans is present in about 37% of OLP lesions. [72] Symptoms of OLP may be exacerbated by candidal overgrowth or infection, while antimycotic treatment can reverse the lesions to the reticular form.

Lundstrom IM, Anneroth GB and Holmberg K [168] **(1984)** studied yeast cultivations from 41 OLP patients and by histological examination in 39 of these cases. Yeasts were found to be present in 19 OLP patients (46%). Candida albicans accounted for over 80% of the yeasts. Amphotericin B was given to 18 OLP patients with positive findings, which resulted in subjective relief of symptoms in 89% of the patients. Clinical improvement was seen in 94%.

Matthews and Scully [169] **(1992)** conducted an open trial to evaluate the efficacy of systemic griseofulvin in OLP treatment. The symptomatic benefit was noted in 21% of the 23 patients, but there was no clinical improvement, and about one-half of the group suffered adverse drug reactions.

E) Antibiotics: Topical tetracycline (doxycycline) was found to be helpful in the treatment of erosive lingual, buccal and gingival OLP lesions in a geriatric patient suffering from the liver disease who did not respond to the topical clobetasol gel application. **(Walchner M, Messer G and Salomon N** [170] **, 1999)**, tetracycline has proven successful in treating OLP in isolated cases, and it may act as an alternative when traditional treatments have proven ineffective.

F) Antimalarials: **Eisen D** [171] **(1993)** conducted an open trial in 10 patients who received 200 to 400 mg of hydroxychloroquine daily as a monotherapy for six months. Patients were evaluated at a baseline and every 4 to 8 weeks during treatment. Nine of ten patients had an excellent response to therapy. Pain relief and erythema were reduced after 1 to 2 months of therapy, but erosions required 3 to 6 months of treatment before they resolved. There were no adverse effects.

G). Phenytoin: There has been only one report of phenytoin therapy in OLP. Two out of 4 OLP cases had complete healing with this drug. No further study has confirmed the efficacy of phenytoin or its side effects, although phenytoin may also induce lichenoid lesions (**Bogaert and Sanchez** [172] **, 1990).**

H) Amitriptyline: Amitriptyline is a tricyclic antidepressant, which could be used to treat LP as depression and anxiety are considered causative agents. **Javadzadeha A, Vatanpourb H, Delavariana Z, *et al*.** [173] **(2008)** compared the mouthwash containing clobetasol, ketoconazole, and amitriptyline with dexamethasone tablet (0.5mg tablet in 5ml water), 30 nystatin drops, and 5ml

diphenhydramine syrup. The new treatment was effective and was better received by the patients with OLP.

I) Amlexanox: Amlexanox is a topical anti-inflammatory drug. It is available in the form of an oral paste (containing 5% amlexanox). Amlexanox paste has substantial anti-inflammatory effects in oral mucosa, with few adverse reactions. It inhibits the development and release of histamine, TNF-alpha, and leukotrienes by inhibiting the degranulation of mast cells.

Fu J, Zhu X, Dan H, *et al.* [174] **(2012)** conducted a randomized, positive-controlled clinical trial in 38 patients with erosive OLP. 20 patients received amlexanox paste (5%) while 18 received dexamethasone paste (0.043%) for 7 days. After seven days of treatment, both groups showed a significant reduction in erosive area and VAS scores. None of the patients had severe hostile reactions. Amlexanox was found equally effective as dexamethasone.

b) NON-PHARMACOLOGICAL MODALITIES

A) Ultraviolet irradiation

Photochemotherapy with 8-methoxypsoralen and long-wave UV-A has been used successfully to treat skin lesions and cutaneous LP. Photochemotherapy with PUVA was first used by **Jansen *et al.*** [175] **(1987)** in a pilot study of OLP, in which all eight patients responded to the treatment. Although oral mucosa seems more resistant than skin to phototoxic damage, PUVA with 8-methoxypsoralen has many side effects such as nausea, dizziness, eye symptoms, paraesthesia, and headache. [137]

Lundquist G, Forsgren H, M, *et al.* [176] **(1995)** investigated the use of PUVA to treat OLP. 18 patients with long-standing, bilateral, severe OLP of the buccal mucosa in the study. A given dose of 0.6 mg/kg 8-methoxypsoralen orally was administered 2 hours before long-wave UV light irradiation was done. The irradiation therapy was administered twelve times at intervals of 2 to 3 days; the patients had received a total average dose of 16.5 J/cm2. Results showed that 13 treated sites compared with six control sites responded significantly favorably to PUVA therapy. They concluded PUVA to be an effective therapy in severe cases of OLP.

B) Low-intensity laser: Low-intensity laser has been used for more than three decades in health care studies. LLLT, also known as photobiomodulation, is a non-invasive, non-pharmacological clinical application, having potential analgesic, anti-inflammatory, immunomodulatory, and biostimulating properties, with minimum adverse effects.

Misra N *et al.* [177] **(2013)** reported a case of a 25-year-old man with a chief complaint of a burning sensation (VAS - 70%) on the buccal mucosa bilaterally on eating hot and spicy food. The patient

was diagnosed with OLP and was treated with a diode laser (940 nm) for symptomatic relief. The treatment was performed for two months, and the patient showed complete remission in the symptoms (VAS- 0%). He was followed up for seven months, and no reappearance of the burning sensation was found. They found diode laser therapy to be effective and a promising alternative in relieving OLP symptoms.

Mutafchieva MZ, Draganova-Filipova MN, Zagorchev PI, *et al.* [178] **(2018)** conducted a study to investigate the effectiveness of biomodulation with diode laser in 12 patients presenting with long-standing erosive-atrophic OLP. All patients received diode laser (810 nm) therapy with the parameters (0.5 W, 30 s, 1.2 J/ cm2) three times a week for a month. Improvement in the clinical signs was achieved in 59.3% of the lesions. Complete resolution was achieved in 37.3% of the lesions. LLLT is a harmless and effective modality for the management of erosive-atrophic OLP.

C) Hyaluronic acid: Hyaluronic acid is a hygroscopic macromolecule formed by the polymerization of glucuronic acid and N-acetylglucosamine disaccharide. It mainly helps heal tissue by activating and moderating the inflammatory responses, promoting cell proliferation, angiogenesis, and migration **(Ialenti A and Di Rosa M** [174] **, 1994)**

A study was performed by **Nolan A, Badminton J, Maguire J *et al.*** [180] **(2009)** to assess the efficacy of a topical hyaluronic acid gel preparation in the management of OLP, found that application of topical hyaluronic acid produced a significant reduction in pain scores when compared with placebo for up to 4 hours post-application. The frequency of application should be increased to obtain a better result as its action is not long-lasting.

D) Reflexotherapy: **Maksimovskaia, Barashkov and Trestsov** [181] **(1991)** report reflexotherapy in OLP treatment. It was conducive to a sooner epithelialization of erosions and ulcers in the buccal mucosa, and its analgesic effect was reasonably high.

E) Surgery: Surgical excision has been recommended for non-healing ulcerative lesions because it provides excellent tissue specimens for histopathologic confirmation of diagnosis and may cure localized disease. **(Emslie ES and Hardman FG** [182] **, 1970).**

Surgical excision in combination with cryosurgery has been used. **Amanat D, Ebrahimi H, Zahedani MZ, *et al.*** [183] **(2014)** studied the effects of cryotherapy with topical corticosteroids in treating 30 OLP patients. A unilateral lesion was chosen from each patient for a single cryotherapy session with nitrous oxide gas, whereas the lesion on the other side received triamcinolone acetonide 0.1% ointment in orabase. The treatment methods, sign score, pain score, and severity of lesions

were significantly reduced in all the follow-up sessions. Cryotherapy with nitrous oxide gas was considered adequate as topical triamcinolone acetonide in OLP treatment with no systemic side effects.

c) NATUROPATHY/HERBAL

A) Curcuminoids: Curcuminoids are the major components of Curcuma longa (turmeric). In India, it has been used for centuries in ayurvedic medicine, as it is non-toxic and has a variety of therapeutic properties, including anti-inflammatory, antioxidant, analgesic, antiseptic activity, and anti-carcinogenic activity **(Maroon JC, Bost JW and Maroon A [184] , 2010)**

Chainani-Wu N, Madden E, Lozada-Nur F, *et al.* [185] (2012) conducted a study to assess the efficiency of curcuminoids in controlling the signs and symptoms of 20 OLP patients doses of 6000 mg/d (3 divided doses) and their safety. The curcuminoid group showed a more significant reduction in clinical signs and symptoms than the placebo group; Adverse effects were uncommon in both groups. Curcuminoids at doses of 6000 mg/d in 3 divided doses are well tolerated and were adequate.

B) Purslane: It is a herbaceous weed from the Portulacaceae family that contains omega-three fatty acids, minerals, β carotene, melatonin, and vitamins A, C, and E. It possesses anti-inflammatory, anti-ulcerogenic, antifungal, and antioxidant properties. The melatonin present in the purslane acts directly as a free radical scavenger stimulating the antioxidant enzymes. Omega-3 fatty acids and melatonin use similar mechanisms to prevent the progression of malignancies. Considering these properties that are beneficial in OLP management may be considered an alternative or supplementary medicine for patients with this disease **(Agha-Hosseini F *et al.* [186] , 2010).**

C) Lycopene: A red-colored carotenoid that gives a red color to tomatoes and several other fruits. It has various therapeutic properties like inhibition of cancer cell proliferation, antioxidant activity, inducing phase II enzymes, interference with growth factor stimulation, regulation of transcription, and restoration of gap junctions **(Levy J and Sharoni Y [187] , 2004).**

Saawarn, Shashikanth, Saawarn, *et al.* [188] (2011) designed a study to assess the efficacy of systemic lycopene in the management of 30 symptomatic OLP patients, who were randomly divided into two groups of 15 each, and were administered lycopene 8 mg/day and an identical placebo, respectively, for eight consecutive weeks. A high (84%) reduction in burning sensation was seen in lycopene than in the placebo group (67%). Lycopene was very efficient in the management of OLP.

D) Aloe vera: It is a cactus-like plant belonging to the Liliaceae family. Its therapeutic properties include antibacterial, anti-inflammatory, antifungal, antiviral, and hypoglycemic effects. It inhibits

the inflammatory process either by reducing the level of TNF-alpha and leukocyte adhesion, or it interferes with the action of the arachidonic acid pathway via cyclooxygenase **(Vogler BK and Ernst E** [189] **, 1999).**

Choonhakarn, Busaracome, Sripanidkulchai *et al.* [190] **(2008)** randomized 54 patients (34 women and 20 men) into two groups to receive Aloe-vera (AV) 70% gel or placebo for eight weeks. 22 of 27 patients treated with AV (81%) had a good response after eight weeks of treatment, while two patients treated with AV (7%) had a complete clinical remission. Burning pain completely diminished in nine patients treated with AV (33%), and symptomatology improved by at least 50% in 17 patients treated with AV (63%). No severe side effects were found in both groups. AV gel can be considered as a safe alternative treatment for patients with OLP.

E) Green Tea: It is a rich source of polyphenols and catechins. It possesses anti-inflammatory and chemopreventive properties. It inhibits antigen presentation, activation, migration, and T-cell proliferation and controls other inflammatory mediators. Hence it may have the potential to manage OLP by modulating antigen mediated specific and non-specific mechanisms involved in the pathogenesis. In addition, green tea consumption may prevent OLP from malignant transformation **(Yoneyama S, Kawai K, Tsuno NH, *et al.*** [191] **, 2008).**

Zhang and Zhou [192] **(2012)** hypothesized that green tea consumption might decrease OLP incidence and be utilized as a safe and economical therapeutic agent.

F) Ignatia: It is extracted from the Strychnosignatii beans and can be used as a remedy in low doses. It is used as a homeopathic cure for the treatment of depression and anxiety symptoms. Hence, it could also be used to manage LP as psychological conditions are considered one of the causative factors **(Mousavi F, Sherafati S and Mojaver YN** [193] **, 2009)**.

3.1.8 RECURRENCE

Recurrence in LP has received little attention in the literature. Although recurrences are common, LP may resolve spontaneously within one to two years.

In a study by **Gupta PC *et al.*** [194] **(1980)**, 1000 males and females were included. Recurrence rates of lichen planus per year in the 10-year follow-up study in the Eruakulam district were studied. With no habit, no recurrence was observed in both the genders. Recurrence was the highest in the mixed habits group, being 4.6%. In the chewing habit group amongst females, recurrence was 3.3%, and in the smoking habit group amongst males, the recurrence rate was 1.8%. The overall recurrence rates were similar for males and females. Interestingly, 11% of the lesions seen in Ernakulam developed

pigmentation signifying impending resolution of the lesion. Pigmentation was reactive and related to the natural course of the lesion.

3.1.9 MALIGNANT TRANSFORMATION OF 'OLP.'

One of the most critical issues concerning OLP is its potential for malignant transformation into OSCC; as cited by **Kramer, Lucas, Pindborg, *et al*.** [130] **(1978),** the WHO has categorized OLP as a precancerous condition. Critics have pointed out that some cases of OLP that progressed to OSCC were misdiagnosed as OLP from the beginning and that lichenoid lesions presenting dysplasia via biopsy should be excluded from the diagnosis of OLP. Therefore modified WHO diagnostic criteria were proposed in 2003.[132]

a) MECHANISM

The mechanisms causing the malignant transformation of OLP are uncertain. A cytokine-based microenvironment arising from chronic inflammation of OLP may induce genetic alterations of epithelial cells to cause malignancy **(Mignogna MD *et al.*** [195] **, 2004)** Such alterations include increased loss of heterozygosity (LOH) at tumor suppressor gene loci, increased deoxyribonucleic acid (DNA) content, and occurrence of aneuploidy. Expression of apoptosis- and cell cycle-regulating proteins such as p53 protein, p21 protein, p16 protein, BCL-2, and bax is also altered in the transformation process. These molecular changes may be helpful in further understanding malignant processes associated with OLP **(Kanemitsu S** [196]**, 2014).**

b) MALIGNANT RISK

The risk of malignant transformation usually varies between 0.4 and 5% over observation periods from 0.5 to 20 years, with a lifetime transformation rate of approximately 1.1%. **(van der Meij EH** [197] **, 1999)**. The preferential sites of OSCC which develop from OLP lesions are the lateral aspect of the tongue and buccal mucosa. Epithelial dysplasia in OLP is predominant in the buccal mucosa. The erosive and atrophic forms of OLP are most likely to progress to OSCC **(Krutchkoff and Eisenberg** [198] **, 1985)**. Interestingly, **Coombes, Cascaini, and Booth** [199] **(2008)** reported a case of an 80-year-old female who had previously been diagnosed with OLP of the tongue dorsum, which transformed into OSCC nearly after ten years.

c) STUDY ARGUMENTS

The menace of malignant transformation of OLP remains a subject of debate in the literature. Some authors accept the possible malignant potential of OLP, while others oppose this suggestion.

Krutchkoff, Culte and Laskowski [200] **(1978)** critically reviewed reports published from 1950-1978 evaluating the premalignant potential of OLP but did not find sufficient documented evidence to support the contention that OLP represents a premalignant condition confidently. A significant problem in this regard was the lack of universally accepted specific diagnostic criteria for OLP.

Eisen D [117] **(2002)** conducted a study to describe the clinical characteristics of 723 patients with biopsy-proven OLP. OSCC developed in 6 patients (0.8%) at sites previously clinically diagnosed as erosive or erythematous OLP.

Van der Meij, Mast and Van der Wall [201] **(2007)** did a 5-year follow-up on 192 patients with OLLs and 67 patients with OLP, selected using the modified WHO diagnostic criteria. 4 cases of OLLs demonstrated the development of OSCC, but no cases of OLP. They were able to identify a subgroup of OLL patients with high malignant potential, with no malignant potential in OLP cases.

Bombeccari GP *et al.* [202] **(2011)** performed a 7-year prospective study to assess the incidence of malignant transformation of 327 OLP patients, in which 229 (70.0%) were women and 98 (30.0%) were men. Eight of 327 patients developed OSCC in OLP areas during a mean follow-up of 81.7 months. Six OSCCs were well-differentiated (75%) and two moderately differentiated (25%). Three subjects (37.5%) developed recurrences within two years. They concluded that OLP was associated with a significant increase in the risk for OSCC.

3.1.10 PROGNOSIS & FOLLOW-UP

For OLP, current immunosuppressive therapies help control signs and symptoms with minimal side effects. The usual clinical course of OLP is lesion tenacity with periods of exacerbation and stagnation. Based on the observed increased risk of malignant transformation of OLP and similar lesions, patients with non-reticular OLP should be regularly followed up 2 to 4 times annually and advised to report if they experience any alterations. [18, 137]

3.2 PROPOLIS

3.2.1 INTRODUCTION

Propolis is a natural resinous mixture that is produced by honeybees utilizing parts of plants, buds, and exudates. Bees collect propolis from different plants in different temperate climatic zones. The word propolis is derived from Greek, in which pro stands for "at the entrance to" and polis for

"community" or "city," which means this natural product is used in hive defense owing to its waxy nature and mechanical properties. Another name of propolis is bee glue. [203]

The color of the propolis may vary from yellowish-green to dark brown, depending on its source and age. Like other waxes, it is hard and brittle when cold but becomes soft and sticky when warmed. Several hundred compounds have been characterized in different propolis types; however, the main chemical constituents of propolis are flavonoids, various phenolic and aromatic compounds, amino acids, minerals, and vitamins A, E, and B complex. These constituents appear in various concentrations depending on geographical location and botanical origin, but the biological effects are similar.[204] A colony of bees collects approximately 150 to 200 g of propolis in one year.[205]

Since ancient times propolis has been significantly employed by a man in topical therapy for cutaneous and mucosal wounds. Due to its antimicrobial, antiviral, antioxidant, and other critical biological properties are widely used in medicine, food and health supplements, dermatological formulations, and even dental products. It is commercially available in capsules, mouthwashes, creams, throat lozenges, and powder.[15]

3.2.2 HISTORICAL BACKGROUND [15-16]

- For ages, propolis has been used in folk medicine to treat several maladies.
- Egyptians used bee glue for "*embalm*ing" their cadavers as it contains putrefactive properties.
- Hippocrates is believed to have used propolis for curing wounds and ulcers. [206]
- Incas employed propolis as an antipyretic agent.
- Greek and Roman physicians have used it as a mouth disinfectant, an antiseptic, and a healing product in wound treatment.
- In the first century after death (AD), Cornelius Celsus wrote about propolis as a drug for promoting suppuration, opening wounds, and treating abscesses.
- Persian manuscripts describe propolis as a remedy against eczemas, myalgia, and rheumatism.
- According to Georgian original medical treatise dated to c. 1486 *Karabadini (Book of medical Treatment),* propolis is considered good against dental decay.
- Propolis has also been called "*Russian penicillin*."
- Propolis was enlisted as an official drug in the London pharmacopeias of the 17th century.
- Towards the end of the 19th century, propolis was widely used. It had been employed in several Soviet clinics for tuberculosis treatment during the Second World War.

- Propolis application has been used to treat wounds and burns, sore throat, and stomach ulcer in Balkan people. [207]

3.2.3 CHARACTERISTICS

Propolis is a lipophilic, hard, and brittle material, and it becomes soft, pliable, gummy, and very sticky when heated, at 25∘C to 45∘C. It usually liquifies at 60∘C to 70∘C. [15]. It acquires a characteristic and pleasant aromatic smell. It also ranges from yellow-green to dark brown, depending on the origin of the resins. However, even transparent propolis has been reported.[208]

3.2.4 CHEMICAL COMPOSITION

Raw propolis is a complex mixture of around 50% resins, 30% waxes, 10% essential oils, 5% pollen, and 5% of various organic compounds. More than 300 constituents were identified in different samples, and new ones are still being recognized during the chemical characterization of various types of propolis. The proportions of the various substances present in the propolis depend upon their place and time of collection. [15,16]

Major propolis constituents include polyphenols; benzoic acids and derivatives; cinnamic alcohol and cinnamic acid and its derivatives; sesquiterpene and triterpene hydrocarbons; benzaldehyde derivatives; other acids and respective derivatives; alcohols, ketones, and heteroaromatic compounds; terpene and sesquiterpene alcohols and their derivatives; aliphatic hydrocarbons; minerals; sterols and steroid hydrocarbons; sugars and amino acids. [209] Sugars are thought to be introduced accidentally during the elaboration of propolis and/or passage of bees over the resin. Some compounds are common in all propolis samples and determine their characteristics properties.[210] Different geographical origins with climatic conditions and specific flora bring variation in propolis's constituents and biological activity. [15,16]

Propolis type	*Geographic origin*	*Plant source*	*Main biactive compounds*
Popular propolis	Europe, North America, non-tropic areas of Asia	Populus spp.	Flavones, flavanones, phenolic acids
Birch propolis	Russia	Betula verrucosa	Flavones and flavonols
Green (rosemary propolis	Brazil	Baccharis spp.	Prenylated p-coumaric acids
Red (clusia propolis)	Cuba, Venezuela	Clusia spp.	Polyprenylated benzophenones
Pacific propolis	Pacific region (Okinawa, Taiwan)	Unknown	C-prenyl flavanones
Canarian propolis	Canary Islands	Unknown	Furafuran lignans

Christov et al.[42]

Figure 2. Geographic origin, primary plant sources, and chemical compounds of propolis **(Christov R, Bankova V, Hegazi A, *et al.* [211] , 1998).**

TABLE 3: Geographic origin, activity, and chemical compounds in Indian scenario.

Sr. no.	Geographic region	Activity	Solvent used in extraction	Reference
1	Karnataka	Antibacterial	Petroleum ether, chloroform, ethanol, methanol, and 40% methanol	[24]
2	West Bengal	Antioxidant	Ethanol and water	[18]
3	Gujarat	Antioxidant, antimicrobial	Ethanol, water, petroleum ether, chloroform, ethanol, methanol, and 40% methanol	[16]
4	Madhya Pradesh	Antimicrobial, hepatoprotective	Ethanol	[33]
5	Maharashtra	Antimicrobial, antibacterial	Ethanol	[34]

Figure 3. Geographic origin, activity, and chemical compounds of propolis in Indian scenario **(Wagh V).** [15]

3.2.5 PROPERTIES

According to **Marcucci M** [208] **(1995); De Castro SL** [210] **(2001) ; Wagh V** [15] **(2013)**

A) Antimicrobial: The mechanism of antimicrobial activity of propolis can be attributed to the synergistic activity between phenolic and flavonoids. The antimicrobial activity has been observed on *Staphylococcus aureus, Streptococcus pyogenes,* gram-positive and gram-negative bacteria species, *Candida Streptococcus mutants*, anaerobic bacteria, and *Mycobacterium T.*

B) Antifungal: Propolis inhibited the growth *of Candida albicans, C. glabrata, Trichosporon spp.*, and *Rhodotorula species.*

C) Antioxidant: The flavonoids concentrated in propolis are potent antioxidants. Antioxidants are known for scavenging free radicals and protecting lipids and water-soluble Vitamin C from being oxidized or destroyed.

D) Anti-Inflammatory: The anti-inflammatory activity can be explained by the presence of active flavonoids and cinnamic acid derivatives. Caffeic acid phenyl ester (CAPE) and caffeic acid (CA) are the fundamental constituents exhibiting this property.

E) Immunomodulatory: Interleukin (IL) -6 is one of the major cytokines that stimulate the Hypothalmic-Pituitary-Adrenal (HPA) axis during inflammatory stress. The immune-stimulating effect of prophylactic propolis treatment has been studied in various clinical studies. **Sforcin, Kaneno and Funari** [212] **(2002)** have concluded that propolis can elicit an enhanced immune reactivity without side effects.

F) Other activities: Propolis also exhibits hepatoprotective, anti-tumoral, anti-protozoan, anti-diabetic properties and used as vaginal applications.

3.2.6 APPLICATIONS OF PROPOLIS IN DENTISTRY

Propolis has been widely used in dentistry; the earliest reference to its use was probably a medical book named 'The Carbadini' published in the 13th century, where its beneficial role had been suggested in tooth decay. Due to the presence of multiple biological properties, propolis has been used for the treatment and periodontal diseases, prevention of dental caries as an interim transport medium for avulsed teeth, for dental hypersensitivity, pulp capping agent, radio-sensitizer in oral oncology (**Wagh V, 2013; Sardana D, InduShekar K, Manchanda S, *et al.*, 2013**; **Kumar R, Channaiah SG, Rastogi T, *et al.* 2017)** [16-17, 213]

APPLICATION IN ORAL LESIONS/CONDITIONS

- **Candidiasis**

Candidiasis is a fungal infection most commonly found in denture wearers and immune-compromised patients. Propolis has been found to inhibit C. Albicans isolated from HIV-seropositive individuals compared to nystatin in this in-vitro study and denture wearers, thus supporting its antifungal activity **(Santos VR, Gomes RT, de Mesquita RA, *et al.* [214] , 2008).**

- **Aphthous Stomatitis**

Samet N, Laurent C, Susarla SM, *et al.* [215] (2008) conducted a pilot study to evaluate the potential of propolis in reducing the number of Recurrent aphthous ulcer (RAU) outbreaks. Patients were

specified to take 500 mg of propolis or a placebo capsule daily. The results showed a significant reduction of outbreaks in the propolis group. Patients in the propolis group also had self-reported a significant improvement in their quality of life.

Ali and Rasool [216] **(2011)** conducted a single-blind clinical study on 120 patients (mean age 39.5 years; 69 women and 51 men over eight months. Propolis buccal paste formulations were prepared and pharmaceutically and clinically evaluated to treat Recurrent Aphthous Stomatitis (RAS) in the study. The patients randomized into the following groups: Group 1 (40 patients) treated with the 1st formula containing Sesame oil based Propolis paste; Group 2 (40 patients) treated with the 2nd formula containing Olive oil-based Propolis paste; Group 3, control group (40 patients) treated with placebo formula containing no active constituent. Patients were instructed to apply the paste directly on the lesion twice daily. Results indicated no allergic reaction or any other side effects. The rate of aphthous ulcer healing was significant with both formulas compared to placebo. The pain withered during the first five minutes of applying the formula, and its disappearance persisted for more than four hours. The period of drug adherence to the oral mucosa in most patients was about 20-30 minutes.

- **Herpes simplex virus (HSV) infection**

Propolis may have a future role in the prophylaxis or treatment of HSV (I) infections of the oral cavity. It prevents the virus absorption into the host cells and/or inhibition of an internal step(s) during the viral replication cycle, thus preventing the appearance and development of symptoms. [15]

Holcová S and Hladiková M [217] **(2011)** conducted a dose-finding study concerning the clinical applicability and tolerability of three different concentrations of Propolis unique extract GH 2002 in a lip balm form (0.1%, 0.5%, and 1%). The trial was proposed as a double-blind, randomized study in 150 outpatients with the onset of Herpes Labialis. The primary parameter was the extent in days, and the second parameter was local pain (assessed on VAS), itching, burning and tension/swelling on a Verbal Rating Scale (VRS), and tolerability. On periodic visits, all three concentrations exhibited highly significant therapeutic results in comparison to the baseline values. The most noticeable effect for the patients was analgesia. The 0.5 % concentration of Propolis unique extract GH 2002 in a lip balm was found to have the best risk-benefit ratio for the treatment of Herpes Labialis.

Jautová J, Zelenková H, Drotarová K, *et al*. [218] **(2019)** conducted a study in which lip cream with unique propolis extract GH 2002 0.5% was used in 199 patients tested against aciclovir 5% in 198 patients suffering from herpes labialis. Upon inclusion, all patients were in the vesicular phase. The application was advised five times daily on the entire upper and lower lip. Propolis was more effective in treating the symptoms and causing complete epithelization of the lesions within three

days compared to 4 days with acyclovir. No allergic reactions, local irritations, or other adverse events occurred.

- **Radiation mucositis**

Noronha VR, Araujo GS, Gomes RT, *et al.* [219] **(2014)** evaluated a mucoadhesive gel containing propolis 5% in 24 adults with cancer during radiotherapy. Patients used the gel a day before the radiotherapy and two weeks after the treatment. By the end of the research, 20 patients did not develop mucositis; two developed oral mucositis Grade 1, and two developed mucositis Grade 2. They concluded that propolis could reduce oral mucositis symptoms and prevent lesions occurrence.

Javadzadeh BA, Pakfetrat A, Tonkaboni A, *et al.* [220] **(2015)** conducted a clinical trial to test a propolis 3% aqueous antiseptic in head and neck cancer patients suffering from radiotherapy-induced mucositis. Their findings indicate it to be a safe and efficient product to prevent and treat radiotherapy-induced mucositis.

- **Repair of oral wounds**

Propolis in aqueous alcohol solution exerted a small analgesic and anti-inflammatory effect and aided in repairing intra-buccal surgical wounds. Topical application of propolis solution was found to accelerate epithelial repair after tooth extraction but did not affect socket wound healing **(Margo and de Carvaho** [221]**, 1990)**.

3.2.7 APPLICATIONS OF PROPOLIS IN THE MANAGEMENT OF 'OLP.'

Propolis exhibits anti-inflammatory, immunomodulatory, and antioxidant properties. This can be very well utilized in resolving the symptoms associated with OLP, like burning sensation and mucosal changes due to immune alteration. Few studies support the above.

Zayada, El-Said, El-Meadawy, *et al.* [222] **(2012)** conducted a study to evaluate the efficacy of topical mucoadhesive gel containing propolis in atrophic and erosive lichen planus patients proved and concluded that it is a promising pharmacological agent for inhibiting epithelial cell proliferation and exhibits anti-inflammatory effect.

Zenouz, Mehdipour, Abadi *et al.* [223] **(2015)** conducted a study to evaluate the effect of propolis on serum levels of IL-17 and clinical symptoms and signs in patients with ulcerative OLP. Serum levels of IL-17, pain and burning sensation severity based on VAS, and the maximum size of the lesions of

25 patients were determined before and after administration of propolis for 30 days (a 500-mg capsule daily). Results showed that administration of propolis significantly decreased IL-17 serum levels, VAS scores, and the maximum OLP lesion sizes.

Joshy, Doggalli, Patil, *et al*. [133] **(2018)** conducted a study to evaluate the efficacy of topical propolis in OLP management. The study consisted of 27 patients with diagnosed symptomatic OLP; 15 patients in the control group, and 12 in the study group. The patients in the control group received 0.1% topical Triamcinolone Acetonide, while the patients in the study group received Propolis gel 5%. Both the groups were evaluated for pain and erythema at baseline (1st visit), first follow‑up (7th day), and second follow‑up (14th day) using NRS and MOMI. The patients in both groups showed a statistically significant improvement in pain and erythema scores from baseline to second follow‑up visit. The topical propolis was found to be as effective as Triamcinolone Acetonide. No adverse reactions were noted. Topical propolis was safe and effective at the prescribed dose, i.e., 5% propolis.

Many studies and clinical trials need to be done further to evaluate the efficacy of propolis in OLP-related lesions.

3.2.8 PROPOLIS ALLERGY

Propolis has a very safe profile and does not exhibit any significant adverse effects. People usually are allergic to raw propolis when an external contact on the skin or mucous membrane is made rather than oral administration. Allergic reactions can occur as contact dermatitis after topical administration in high concentration. Few manifestations include rhinitis and/or conjunctivitis. Rare cases of respiratory distress, headache, and nausea have been reported **(Chan GC, Cheung KW and Sze DM** [224]**, 2013).** That is why propolis in low concentrations or doses is wholly recommended for safe use as it provides excellent therapeutic benefit owing to its biological properties.

MATERIALS & METHODS

PLACE OF THE STUDY

The study participants comprised of dental outpatients visiting the **Department of Oral Medicine and Radiology, Babu Banarasi Das College Of Dental Sciences**, Babu Banarasi Das University, Lucknow, Uttar Pradesh. Ethical clearance for the dissertation was obtained from the Institutional Ethical Committee (IEC code – 08; BBDCODS/01/2019), in accordance with, the declaration of Helsinki, research involving human subjects.

STUDY PARTICIPANTS & SAMPLE SIZE

For the study purpose 30 (thirty) participants will be enrolled, and divided into two study groups i.e. Group A and Group B. **Group A** consisting of 15 subjects on whom **5% topical Propolis** will be used. **Group B** consisting of 15 subjects on whom **0.1% topical Tacrolimus** will be used. The subjects of either gender, satisfying the eligibility criteria and those willing to participate in the study were selected for the study.

ELIGIBILITY CRITERIA

A.) INCLUSION CRITERIA:

- Patients who are well oriented to time, place and person.
- Individuals willing to be a part of the study, who sign the informed consent form, and who find it convenient to appear for follow-ups as required by the study.
- Patients of either gender aged between 18-65 years.
- Patients with clinically diagnosed symptomatic OLP (based on modified WHO clinical criteria, 2003).[132]
- Patients who had not used systemic or topical medications (glucocorticosteroids) for at least 1 month.
- Patients who agree not to use any other medication such as analgesics and anesthetics in either topical form or systemic form during the study.

B.) EXCLUSION CRITERIA:

- Patients not willing to be a part of the study or failing to give their consent.

- Patients suffering from any systemic disease.
- Patients with lichenoid lesions thought to arise as a hypersensitivity reaction to drugs/medications and dental materials.
- Patients on long-term glucocorticosteroid therapy.
- Pregnant and lactating patients.
- Patients allergic to bee products.

SAMPLING METHOD

1. The study were to comprise of 30 individuals within the age group of 18-65 years, clinically diagnosed with symptomatic Oral Lichen Planus.
2. The subjects to be selected according to the inclusion and exclusion criterion.
3. A detailed case history of each participant to be recorded using a case history proforma.
4. Following the establishment of the diagnosis, each patient to be informed about the protocol and given the appropriate instructions after obtaining a written consent.

RANDOMIZATION

All the patients (30) to be included in the study were to be randomly divided (double-blinded) into two groups A and B (consisting of 15 patients each).

ALLOCATION

The principal investigator was to carry out the initial as well as periodic evaluations of all study participants.

ARMAMENTARIUM

(Materials and Equipments used in the study with specifications and company)

MATERIALS

1. PROPOLIS

Organic and raw Propolis was procured from the apiary of the company: SAFA HONEY CO. (19/2, Mango Garden Layout, Kanakpura Road, Bangalore- 560062)

Figure 4: Raw bee propolis

- PREPARATION OF PROPOLIS GEL (5%)

- The raw Propolis procured from the above mentioned company was formulated into a gel form at the multidisciplinary research laboratory CSIR-CDRI (Council of Scientific and Industrial Research-Central Drug Research Institute), Lucknow

- Concerned Departments:

1. Department of Pharmaceutics and Pharmacokinetics
2. Department of Microbiology

Figure 5: Department of Pharmaceutics and Pharmacokinetics, CSIR-CDRI, Lucknow

- Equipments used:

Beaker, Conical Flask, Measuring cylinder, Glass rod, Spatula, Filter paper, Funnel, Aluminium foil, Digital weighing balance, Magnetic stirrer and Propeller mixer.

- Chemicals used:

Ethanol, starch powder, carbopol934, triethanolamine (TEA), methylparaben, propylparaben and peppermint oil

- Preparation:

The preparation method applied is as follows, similar to **Joshy *et al*.** [133]

- The propolis was properly cleaned and cut into small pieces.
- A sterilized 1000 ml beaker was filled with 500 ml of absolute alcohol and approximately 500 g of cleaned propolis was added to it. After covering the beaker with aluminum foil, it was kept in a warm dark place for seven days to achieve complete extraction.
- Post seven days, the contents of the beaker were filtered using the filter paper in a conical flask and the solution was again transferred to a clean beaker. It was then subjected to evaporation by using the magnetic stirrer for removing excess of the solvent, while maintaining the temperature at 40°C.

- The resultant thick, dark brown colored, liquid of approzimately 100 ml was obtained to which 500 gm of starch (99% pure) was added, to remove the stickiness and obtain a powder form.
- 1% carbopol solution (2 gm in 200 ml of water) was prepared separately in a sterilized beaker to which 0.40g of methylparaben, 0.30g of propylparaben, and 0.75ml of peppermint oil (flavouring) was added and stirred continuously to obtain a homogenous mixture.
- The starch-propolis powder was then added to the mixture and further homogenized using a propeller mixer at the speed of 250 rpm for 15minutes. Thereafter, 1ml of TEA (neutralizing agent/ thickening agent) was added to thicken the solution into a gel like consistency.

Figure 6: Sample of the final product i.e, propolis gel (5%)

- Finally, the preparation was packed in preweighed sterilized aluminium tins and sealed. It was packed in such a way that 1 aluminium tin contained 25 gms of the formulation and 1gm of the formulation consisted 0.2 gm of the extract. Therefore, each aluminium tin comprised of 5gms of propolis extract.

Figure 7: Preweighed sterilized aluminium tin used to dispense propolis gel (5%)

- The aluminium tin was given to each participant falling in the Group A, for the application.

2. TACROLIMUS (0.1%)

0.1% topical Tacrolimus gel was commercially purchased and applied by the study participants, falling in Group B.

Brand: Tacvido (0.1%) Forte Oral Gel 25 ml

Manufactured By: MOHRISH PHARMACEUTICALS

Figure 8: Commercial product of tacrolimus (0.1%) containing oral gel

FOR CLINICAL EXAMINATION

1. Sterile gloves
2. Disposable mouth masks
3. Sterilized kidney trays
4. Sterilized intraoral mouth mirrors
5. Sterilized periodontal probe
6. Sterilized intraoral explorer
7. Sterilized tweezers
8. Sterilized cotton holder
9. Sterilized cotton

Figure 9: Armamentarium for intraoral clinical examination of the study patients

METHODOLOGY

A total of 24 patients were enrolled in the study who gave consent to particpate and met the eligibility criteria. A detailed history and clinical findings were recorded in individual proformas designed especially for the study on the baseline visit. However, eventually 4 patients dropped out self willingly after the baseline visit and were disregarded as study participants. Thereafter, only 20 patients were considered for full assessment.

The study participants were divided into 2 groups.

- **Group A:** Consisting of 10 participants
- **Group B:** Consisting of 10 participants

BASELINE VISIT PATIENT ASSESSMENT

All the relevant readings for all clinical parameters for each patient from baseline to subsequent visits were recorded and entered in the proforma.

1. Burning sensation score for Oral Lichen Planus was considered using the Visual Analogue Scale (VAS) [123] ranging from: 0 (no burning sensation), 5 (burning sensation on eating hot and spicy food) to 10 (worst burning sensation occuring spontaneously.

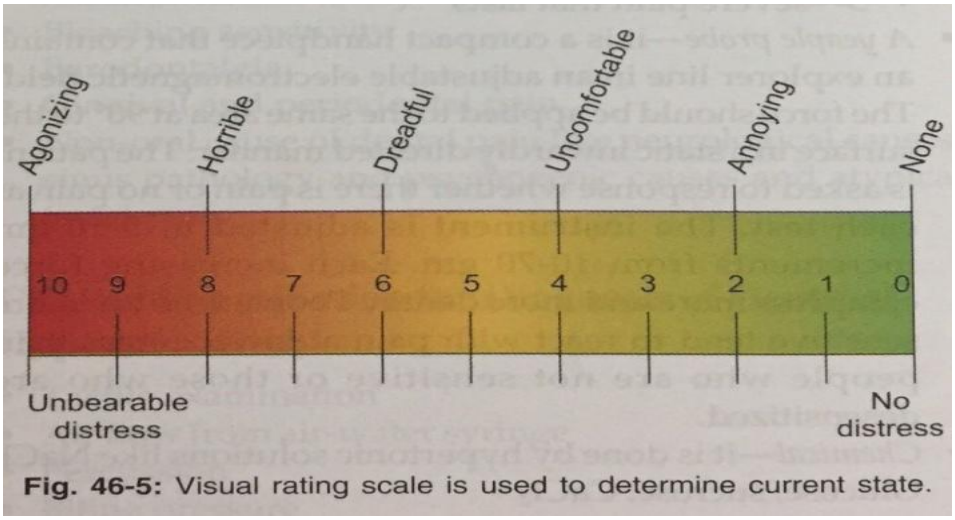


Fig. 46-5: Visual rating scale is used to determine current state.

Figure 10: Visual analogue scale (VAS) used to measure intensity of the burning sensation in the study participants.

2. Duration of the lesion was noted.

DURATION
>1 year
1-5 years
5-10 years
>10 years

3. The clinical signs of OLP were measured using a semi-quantitative scale, Modified Oral Mucositis Index (MOMI), [123] validated for measurement of clinical signs of OLP.

An intensity score for erythema ranging from 0 to 3 was used:

0 = normal,

1= mild erythema,

2 = moderate erythema,

3 = severe erythema.

The score for ulcerations was based on area of ulceration:

0= no ulcerations,

1 = between 0-0.25 cm^2,

2 = between 0.25-1 cm^2,

3 = $\geq$ 1 cm^2.

Different peri/intraoral sites were evaluated including lips, labial mucosa (upper and lower), buccal mucosa (right and left), vestibule (maxillary/ mandibular right and left), lateral borders of the tongue (right and left), dorsum of the tongue (right and left), ventral surface of the tongue, floor of the mouth (right and left), maxillary gingiva (right and left), soft palate hard palate, retromolar area, alveolar ridge/mucosa, and faucial pillars. The scores for erythema and ulceration was obtained by summing the respective scores for these sites and the total score for clinical signs was obtained by summing the erythema and ulceration scores.[123]

ACTIVE PHASE

The subjects were blinded i.e. the subjects were not aware of the nature of the drug they were receiving.

Patient regime:

- Group A shall receive topical Propolis 5% while the patients in Group B shall receive 0.1% topical Tacrolimus gel.
- The patients will be instructed to apply the gel on the lesion twice a day for 30 days and refrain from eating, drinking and rinsing for at least 30 min after the topical application.
- Patients were asked to report immediately in case they encounter any adverse effects and they were managed on a case to case basis.
- In the active phase, the patients will be assessed for the effectiveness of topical applications in resolving the lesion and reducing burning sensation on the **7^{th}, 14^{th}, 21^{st}, 28^{th} day.**

FOLLOW UP PHASE

- The follow-up phase comprised of 3 months in total.
- Patient were followed up after at interval of 1 month each and noted for any recurrent lesions and associated resolution of such lesions.

Patient of Group A (Propolis)

- Day 1

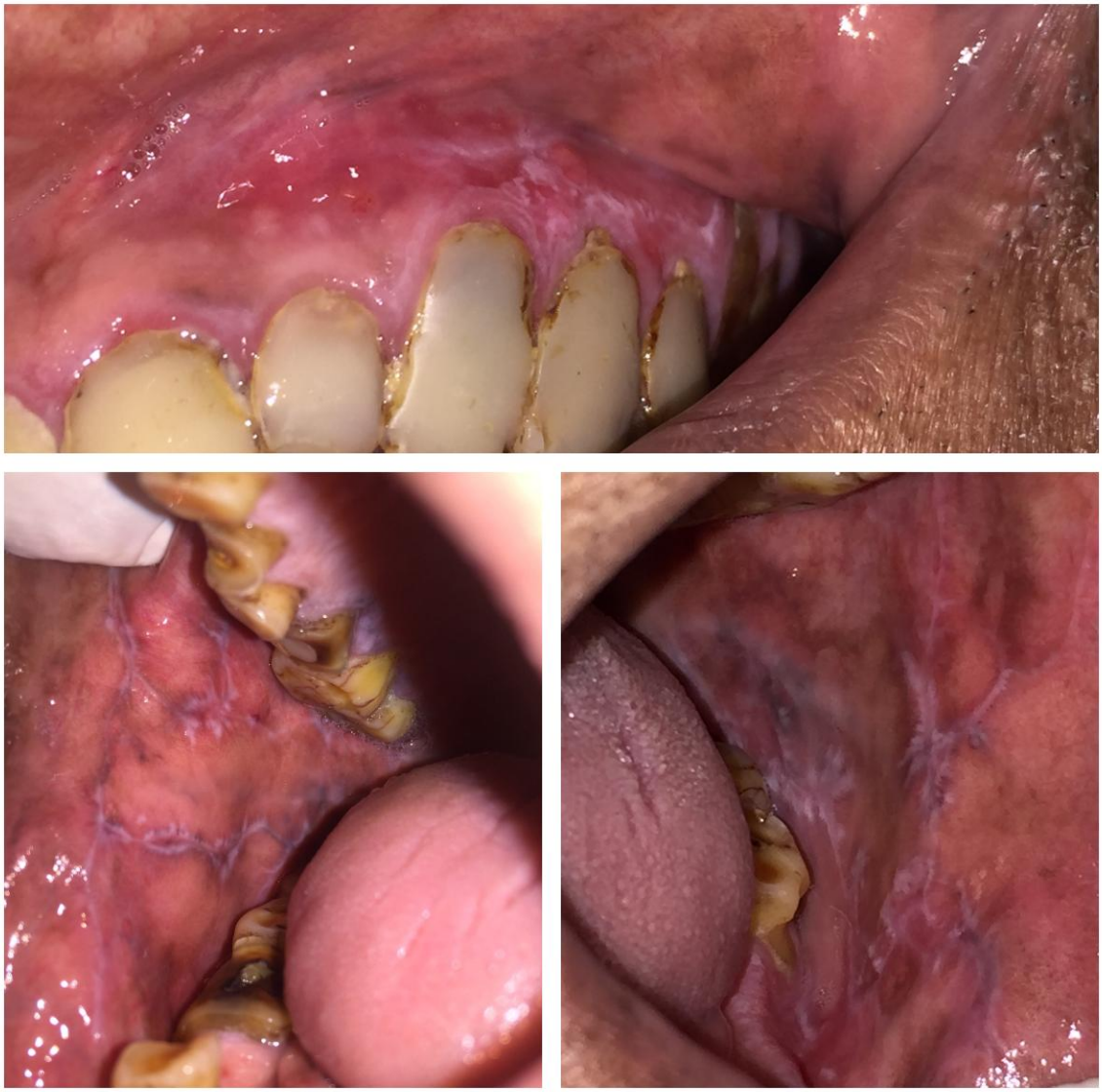


Figure 11: Baseline visit assessment of the patient (Group A)

- After 4 weeks

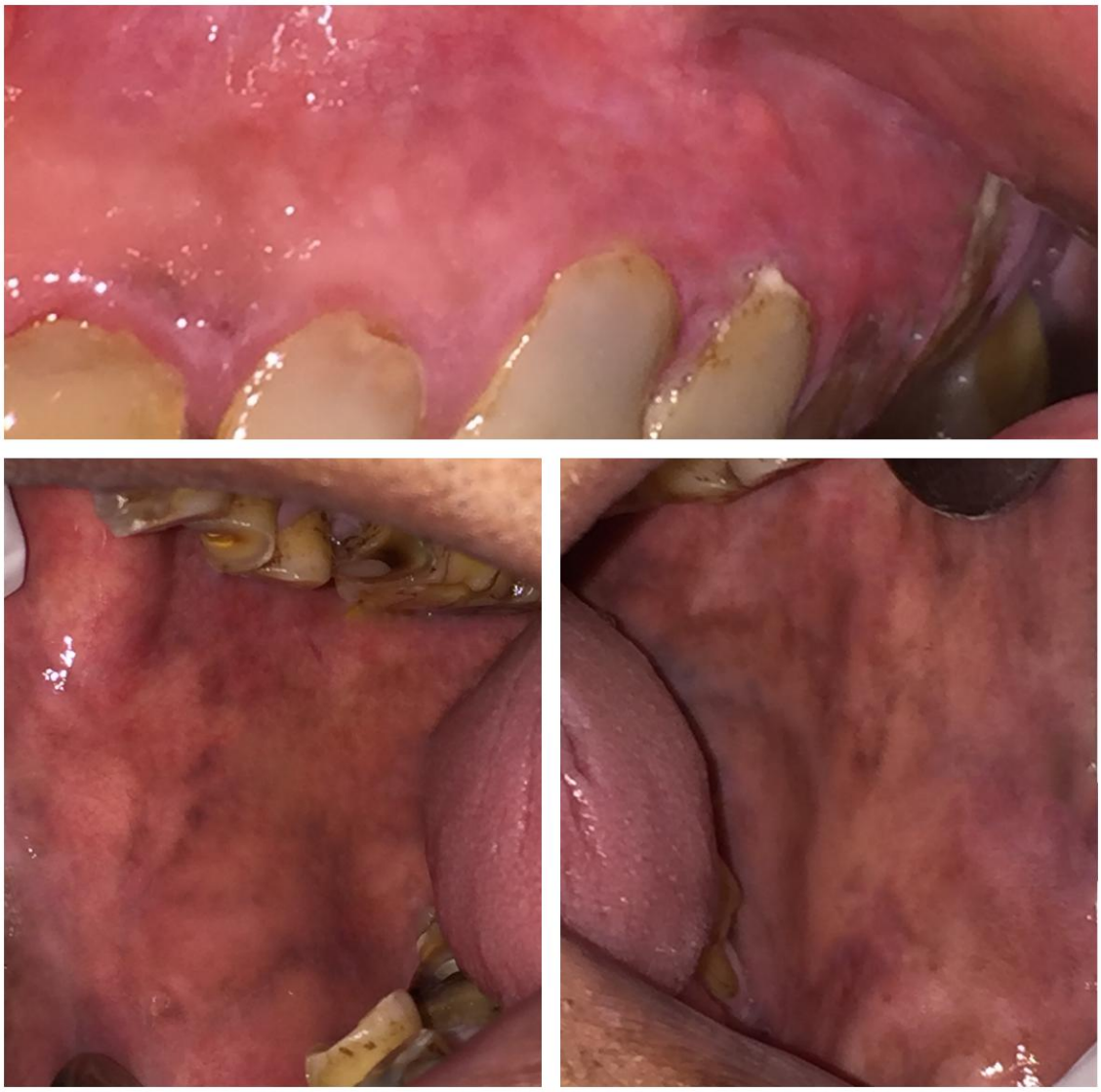


Figure 12: Assessment of the patient (Group A), at the end of active phase.

- After 12 weeks

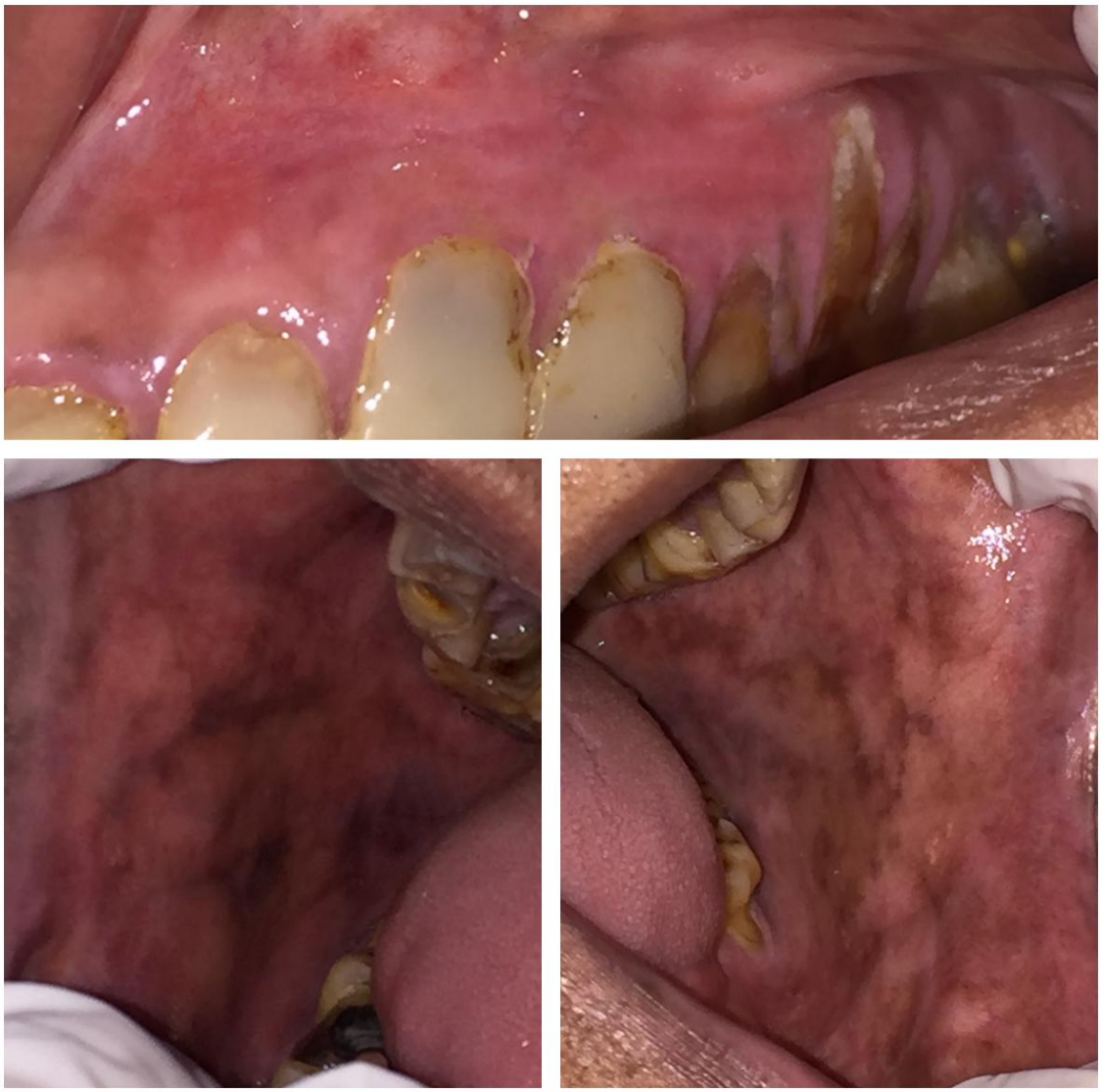


Figure 13: Assessment of the patient (Group A), on the 3rd follow-up.

Patient of Group B (Tacrolimus)

- Day 1

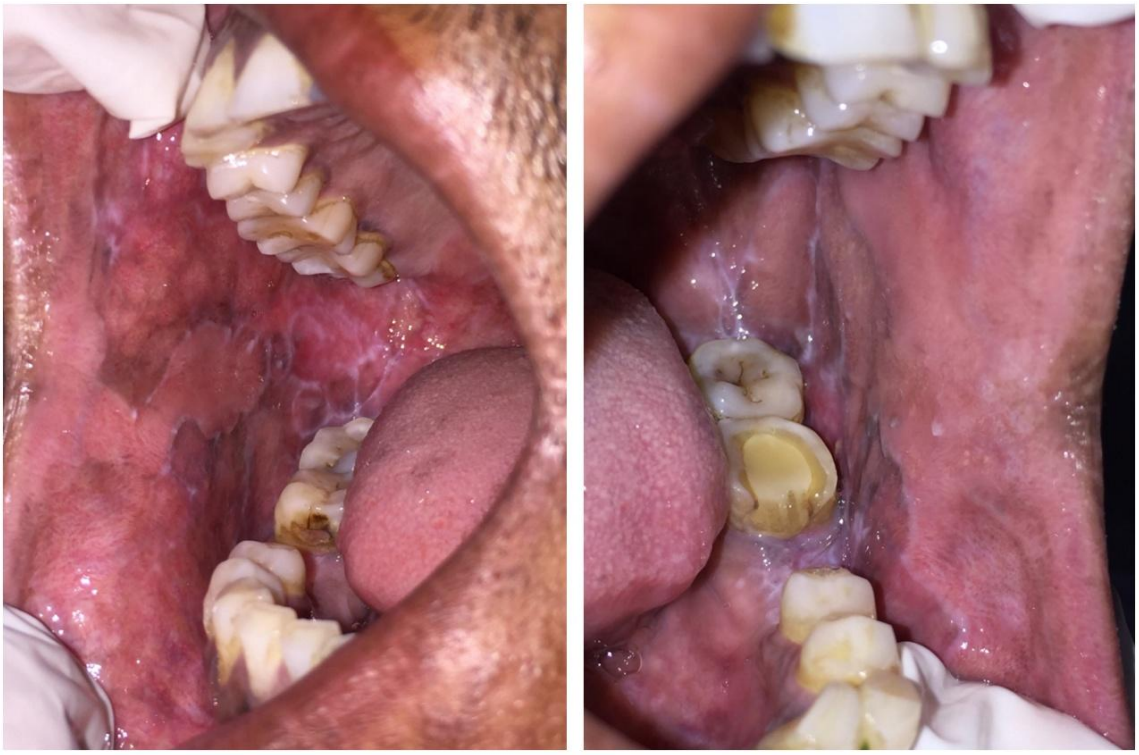


Figure 14: Baseline visit assessment of the patient (Group B)

- After 4 weeks

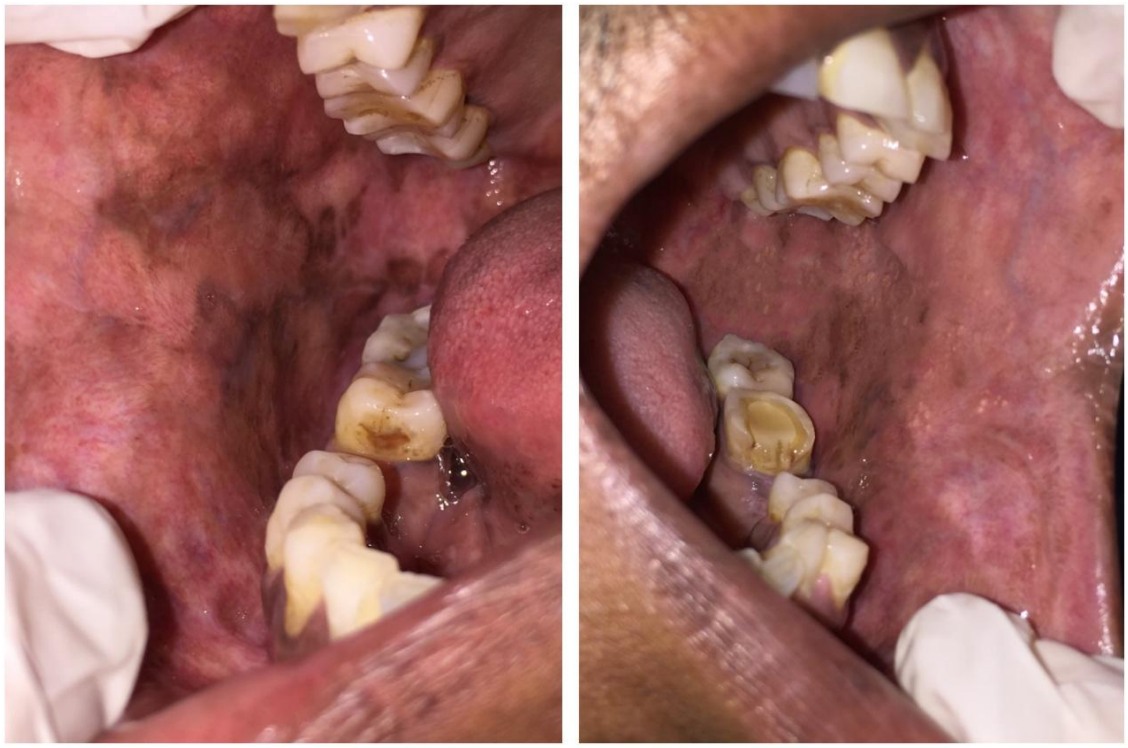


Figure 15: Assessment of the patient (Group B), at the end of active phase.

- After 12 weeks

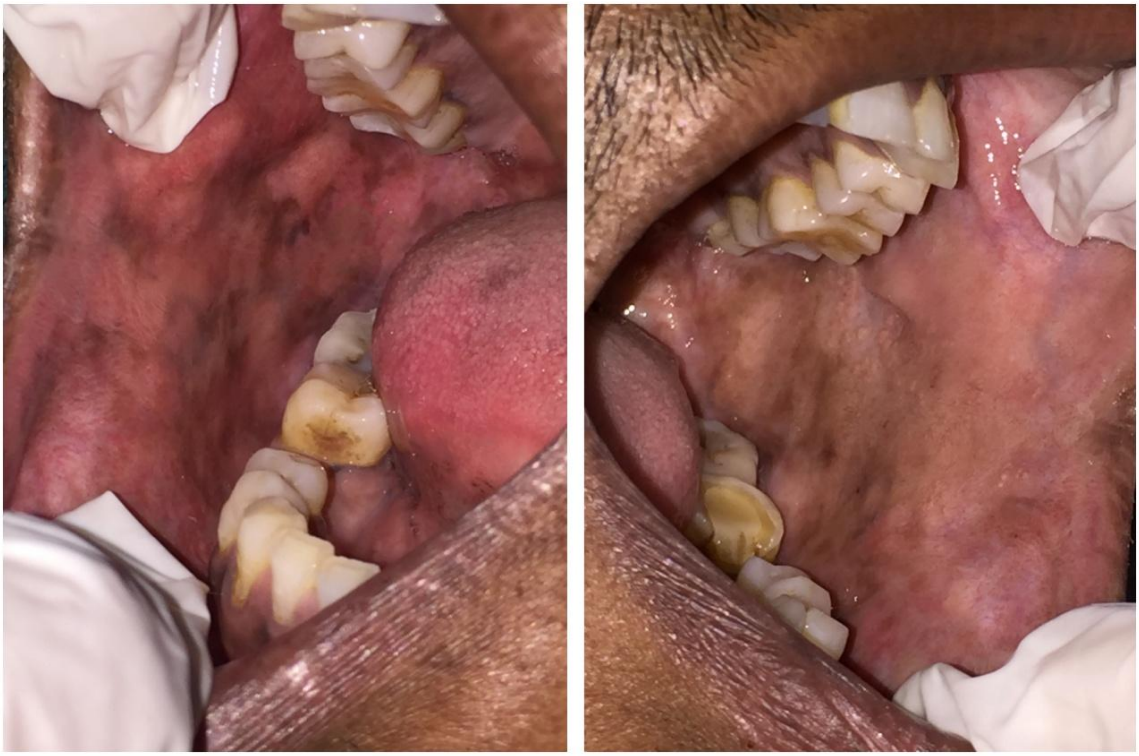


Figure 16: Assessment of the patient (Group B), on the 3rd follow-up.

STATISTICAL ANALYSIS

The data was entered into the computer using Microsoft excel, tabulated and subjected to statistical analysis using SPSS software for windows. Accordingly results were drawn based on the study objectives.

RESULTS

PLACE OF STUDY

The present study was conducted in the Department of Oral Medicine & Radiology, Babu Banarasi Das College Of Dental Sciences, Babu Banarasi Das University, Lucknow, to do a comparative evaluation of the efficacy of topical propolis and tacrolimus in symptomatic oral lichen planus patients.

After full assessment and on the basis of willingness to participate in the study, both the groups comprised of 10 participants each. Group A was given topical Propolis 5% while Group B was given 0.1% topical Tacrolimus gel. The patients were instructed to apply the gel on the lesion twice a day for 30 days and periodic assessment was done at the interval of 7^{th}, 14^{th}, 21^{st} and 28^{th} day, during the month of active phase of the medication. Post this, patients were followed up after at interval of 1 month each for a total of 3 months, and noted for any recurrent lesions.

DATA ANALYSIS

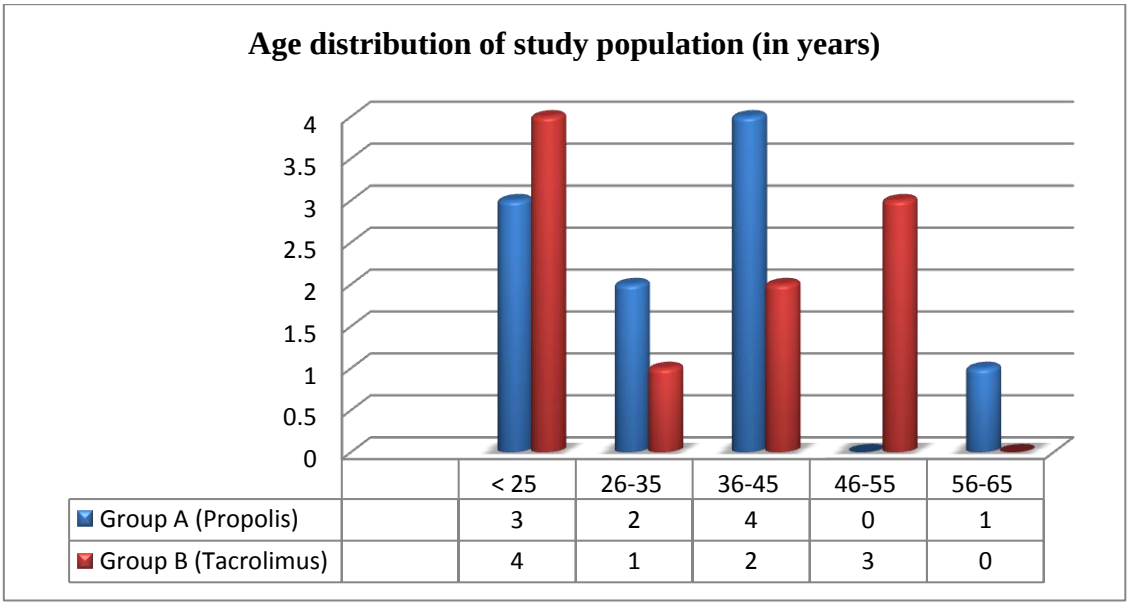
The data obtained was entered into spread sheets and analysed using SPSS software 23.0 version (IBM; Chicago). The variables are presented in mean and standard deviation. Independent sample t-test or student t-test was run to determine significant differences in burning sensation (VAS) scores, erythema, ulceration, pigmentation and recurrence between the groups of Propolis and Tacrolimus at different time periods. Repeated measures ANOVA test was applied to compare pairwise comparison for assessing further significance. P value lower than 0.05 was considered to be statistically significant. The results obtained and observations made were as follows:

AGE DISTRIBUTION OF STUDY PARTICIPANTS

The patients enrolled in the study fell in the age range of 18-65 years. They were sub-grouped into 5 categories: below 25 years, 26-35 years, 36-45 years, 46-55 years and 56-65 years.

GROUP A: This group comprised of 10 patients. There were 3 (30%) patients in the age range below 25 years; 2 (20%) patients in the group of 26-35 years, 4 (40%) patients in the group of 36-45 years, 0 (0%) patients in the group of 46-55 years, and 1 (10%) patient in the group of 56-65 years (Graph 1).

GROUP B: This group comprised of 10 patients. There were 4 (40%) patients in the age range below 25 years; 1 (10%) patient in the group of 26-35 years, 2 (20%) patients in the group of 36-45 years, 3 (30%) patients in the group of 46-55 years, and 0 (0%) patient in the group of 56-65 years (Graph 1).



Graph 1: Age distribution in both the groups

Clearly a dominance was observed in younger age group i.e. below 25 years, in both the groups or overall study participants. However, both the groups had similar age group pattern due to equal number of participants, with no significant difference between them with a value of (p= 0.908) (Table 3).

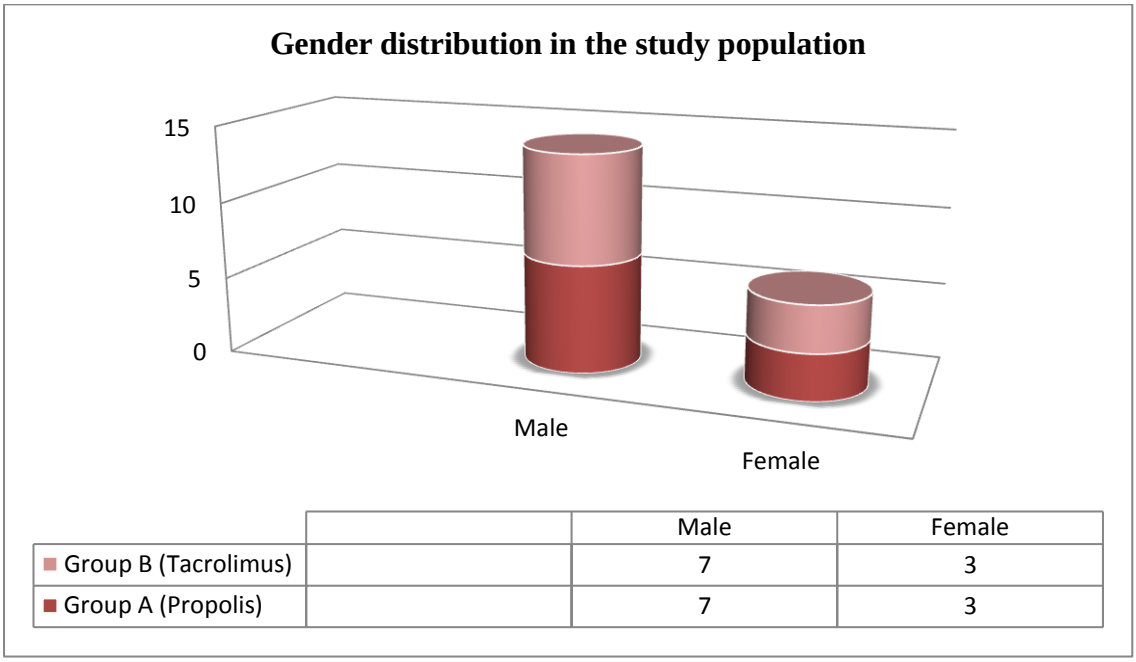
Table 3: Age distribution of the study population

Groups	N	Mean + S.D	F test	P value
Propolis	10	34.70 ± 13.83	0.014	0.908 (NS)
Tacrolimus	10	35.40 ± 12.72		

** = Highly Significant; * = Significant; NS = Nothing Significant

GENDER DISTRIBUTION OF STUDY PARTICIPANTS

There were 7 (70%) males and 3 (30%) females in both the groups A and B. A clear male predilection was noted in both groups, but a uniform distribution of males and females across them (Graph 2).



Graph 2: Gender distribution in both the groups

Chi- square test was applied to see the distribution. A value of (p= 1.000) was obtained stating no significant statistical differences (Table 4).

Table 4: Gender distribution of the study population

Gender	Propolis N (%)	Tacrolimus N (%)	Total	Chi square test	P value
Males	7 (35.0)	7 (35.0)	14 (70.0)	0.000	1.000 (NS)
Females	3 (15.0)	3 (15.0)	6 (30.0)		
Total	10 (50.0)	10 (50.0)	20 (100)		

** = Highly Significant; * = Significant; NS = Nothing Significant

EFFECT OF TOPICAL MEDICATIONS ON BURNING SENSATION

Clinically burning sensation scores for Oral Lichen Planus were recorded using the Visual Analogue Scale (VAS) ranging from 0 to 10, on baseline visit, during each visit of the active phase and on each follow up visit (in case of recurrent lesions). To make the results less cumbersome, the respective VAS scores during each visit of the active phase were summed up and the total score at the end of active phase was obtained for each patient. Table 5 & 6. depict cumulative scores of all the 10 patients at baseline, end of active phase and follow ups (FU1, FU2, FU3). In this min. and max. values were considered and mean values were obatined. Graphs 3 and 4. also depict bar charts showing the VAS distributions.

PROPOLIS (Group A)

Baseline visit

At the baseline out of the 10 patients, 4 (40%) patients had a score of 7, 2 (20%) patients had a score of 5 and rest 4 (40%) patients had a score of 4, 6, 9 and 10 each. The mean value at the baseline was 6.700 ± 1.82 (Table 5).

Active Phase (1st visit to 4th visit)

At the end of active phase, out of the 10 patients, 9 (90%) patients had a score of 0 i.e. completely asymptomatic, however only 1 (10%) patient had a score of 1. The mean value at the end of active phase was 0.1000 ± 0.316 (Table 5).

1st Follow Up

On 1st follow up i.e. after 1 month of end of active phase, out of 10 patients, 3 (30%) patients started experiencing burning sensation again due to recurrence of the lesions with a score of 1, 5, and 9 each., while 6 (60%) patients were completely asymptomatic with a score of 0. 1 (10%) patient did not turn up. The mean value on 1st follow up was 1.500 ± 3.06 (Table 5).

2nd Follow Up

On 2nd follow up i.e. after 1 month of 1st follow up, out of 10 patients, 2 (20%) patients showed improvement with a score of 2 and 5 each, while 6 (60%) patients were completely asymptomatic with a score of 0. 2 (20%) patients did not turn up. The mean value at the end of active phase was 0.600 ± 1.577 (Table 5).

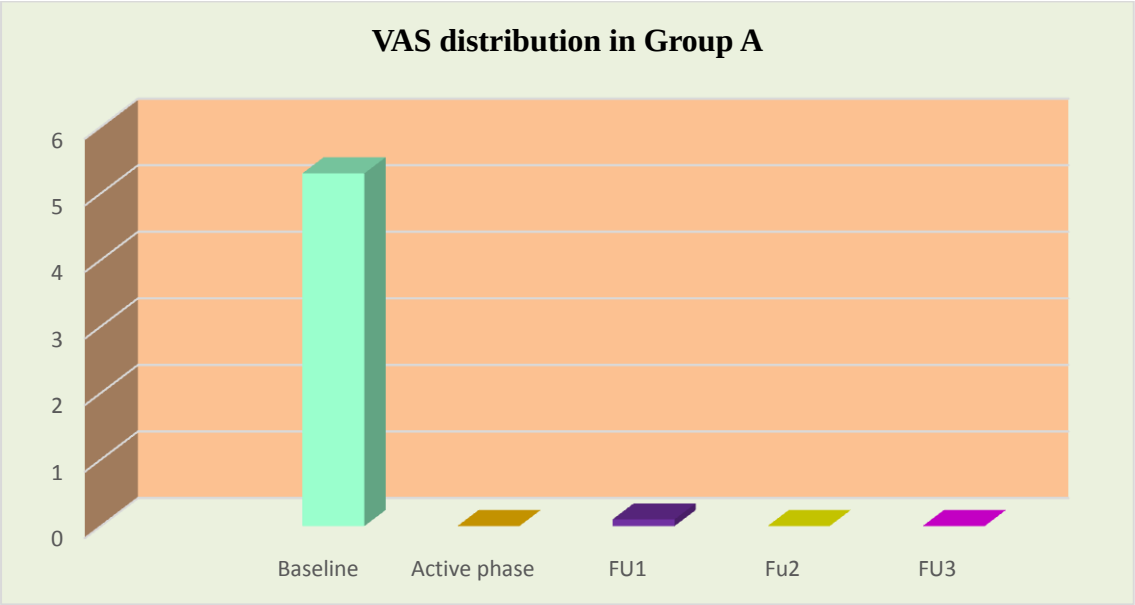
3rd Follow Up

On 3rd follow up i.e. after 1 month of 2nd follow up, out of 10 patients, only 1 (10%) patient was still symptomatic with a score of 2, while 7 (70%) patients were completely asymptomatic with a score of

0. 2 (20%) patients did not turn up. The mean value at the end of active phase was 0.200 ± 0.632 (Table 5).

Table 5: Distribution of Burning sensation (VAS) Scores in Group A

Visits	N	Minimum	Maximum	Mean ± S.D
Baseline	10	4.00	10.00	6.700 ± 1.82
Active phase (end)	10	.00	1.00	0.1000 ± 0.316
FU1	10	.00	9.00	1.500 ± 3.06
FU2	10	.00	5.00	0.600 ± 1.577
FU3	10	.00	2.00	0.200 ± 0.632



Graph 3: Distribution of Burning sensation (VAS) Scores in Group A

Repeated measures ANOVA with a Green house Geisser correction determined that mean VAS scores differed statistically significantly between the points ($F = 32.643$, $p<0.001$). Post hoc tests using Bonferroni correction revealed that VAS reduced greatly from baseline to follow up period. Table 6. shows pairwise comparison for VAS scores across the time intervals.

Table 6: Pairwise comparison for VAS scores across time intervals (Group A)

(I) factor1	(J) factor1	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b]	
					Lower Bound	Upper Bound
Baseline	Active phase	6.600*	.521	.000	4.679	8.521
	FU1	5.200*	1.181	.017	.841	9.559
	FU2	6.100*	.849	.001	2.967	9.233
	FU3	6.500*	.671	.000	4.025	8.975
Active phase	Baseline	-6.600*	.521	.000	-8.521	-4.679
	FU1	-1.400	.991	1.000	-5.057	2.257
	FU2	-.500	.522	1.000	-2.425	1.425
	FU3	-.100	.233	1.000	-.961	.761
FU1	Baseline	-5.200*	1.181	.017	-9.559	-.841
	Active phase	1.400	.991	1.000	-2.257	5.057
	FU2	.900	.526	1.000	-1.041	2.841
	FU3	1.300	.803	1.000	-1.665	4.265
FU2	Baseline	-6.100*	.849	.001	-9.233	-2.967
	Active Phase	.500	.522	1.000	-1.425	2.425
	FU1	-.900	.526	1.000	-2.841	1.041
	FU3	.400	.306	1.000	-.727	1.527
FU3	Baseline	-6.500*	.671	.000	-8.975	-4.025
	Active phase	.100	.233	1.000	-.761	.961
	FU1	-1.300	.803	1.000	-4.265	1.665
	FU2	-.400	.306	1.000	-1.527	.727

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

TACROLIMUS (Group B)

Baseline visit

At the baseline out of the 10 patients, 2 (20%) patients had a score of 4, 2 (20%) patients had a score of 5, 2 (20%) patients had a score of 6, and rest 4 (40%) patients had a score of 2, 3, 8 and 10 each. The mean value at the baseline was 5.300 ± 2.359 (Table 7).

Active Phase (1st visit to 4th visit)

At the end of active phase, out of the 10 patients, all the patients (100%) had a score of 0 i.e. completely asymptomatic. The mean value at the end of active phase was 0.0000 ± 0.000 (Table 7).

1st Follow Up

On 1st follow up i.e. after 1 month of end of active phase, out of 10 patients, only 1 (10%) patient started experiencing burning sensation again due to recurrence of the lesions with a score of 1, while 9 (90%) patients were completely asymptomatic with a score of 0. The mean value on 1st follow up was 0.100 ± 0.316 (Table 7).

2nd Follow Up

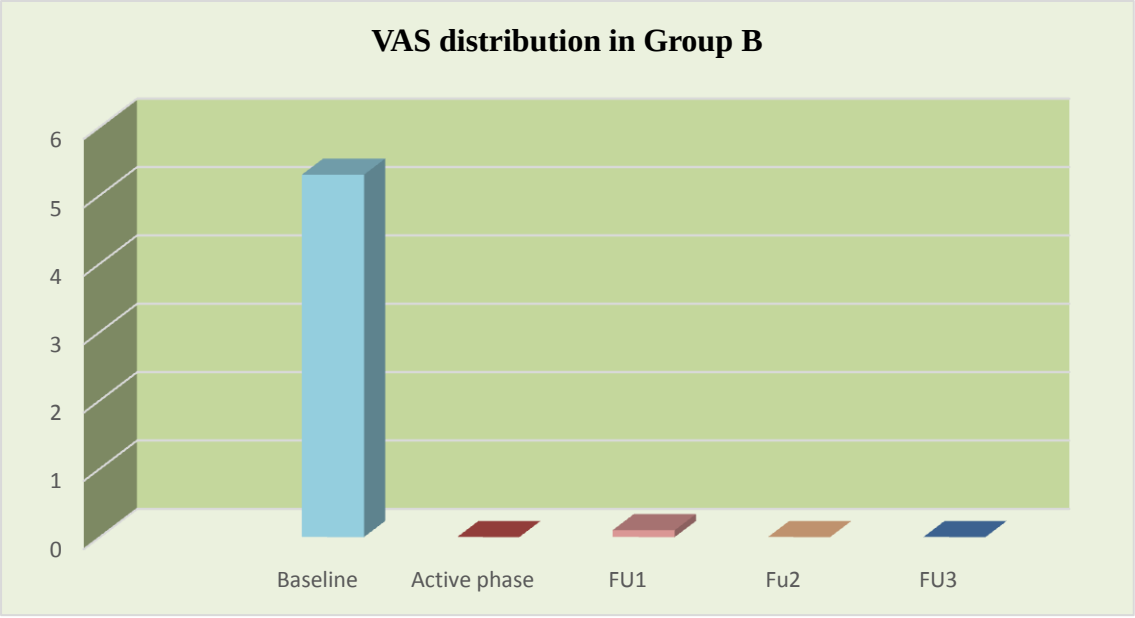
On 2nd follow up i.e. after 1 month of 1st follow up, out of 10 patients, 9 (90%) patients were completely asymptomatic with a score of 0. 1 (10%) patient did not turn up. The mean value at the end of active phase was 0.0000 ± 0.000 (Table 7).

3rd Follow Up

On 3rd follow up i.e. after 1 month of 2nd follow up, out of 10 patients, 8 (80%) patients were completely asymptomatic with a score of 0. 2 (20%) patients did not turn up. The mean value at the end of active phase was 0.0000 ± 0.000 (Table 7).

Table 7: Distribution of Burning sensation (VAS) Scores in Group B

Visits	N	Minimum	Maximum	Mean ± S.D
Baseline	10	2.00	10.00	5.300 ± 2.359
Active phase	10	.00	.00	0.0000 ± 0.000
FU1	10	.00	1.00	0.100 ± 0.316
FU2	10	.00	.00	0.0000 ± 0.000
FU3	10	.00	0.00	0.0000 ± 0.000



Graph 4: Distribution of Burning sensation (VAS) Scores in Group B

Repeated measures ANOVA with a Green house Geisser correction determined that mean VAS scores differed statistically significantly between the points ($F = 27.958$, $p<0.001$). Post hoc tests

using Bonferroni correction revealed that VAS reduced greatly from baseline to follow up period. Table 8. shows pairwise comparison for VAS scores across the time intervals.

Table 8: Pairwise comparison for VAS scores across time intervals (Group B)

(I) factor1	(J) factor1	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b]	
					Lower Bound	Upper Bound
Baseline	Active phase	5.300*	.746	.001	2.547	8.053
	FU1	5.200*	.680	.000	2.692	7.708
	FU2	5.300*	.746	.001	2.547	8.053
	FU3	5.300*	.746	.001	2.547	8.053
Active phase	Baseline	-5.300*	.746	.001	-8.053	-2.547
	FU1	-.100	.100	1.000	-.469	.269
	FU2	.000	.000	.	.000	.000
	FU3	.000	.000	.	.000	.000
FU1	Baseline	-5.200*	.680	.000	-7.708	-2.692
	Active phase	.100	.100	1.000	-.269	.469
	FU2	.100	.100	1.000	-.269	.469
	FU3	.100	.100	1.000	-.269	.469
FU2	Baseline	-5.300*	.746	.001	-8.053	-2.547
	Active Phase	.000	.000	.	.000	.000
	FU1	-.100	.100	1.000	-.469	.269
	FU3	.000	.000	.	.000	.000
FU3	Baseline	-5.300*	.746	.001	-8.053	-2.547
	Active phase	.000	.000	.	.000	.000
	FU1	-.100	.100	1.000	-.469	.269
	FU2	.000	.000	.	.000	.000

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

b. Adjustment for multiple comparisons: Bonferroni.

GROUPS COMPARISON

Student-t test was applied to find differences in VAS scores between Propolis and Tacrolimus groups. No significant difference was noted in any time interval. Over all pain score reduced from a mean of 6.700 $\pm$ 1.828 to 0.200 $\pm$ 0.632 in the Propolis group from baseline to follow up of third

month. The mean score in the Tacrolimus group reduced from 5.300 ± 2.359 to 0.000 ± 0.000 from baseline to follow up of third month.

Observation:

Between both the groups, Tacrolimus showed a better response in reducing burning sensation, compared to Propolis. There was statistically significant (p = 0.000) improvement in the VAS scores. Table 9. shows distribution of burning sensation scores between both the groups across the time intervals.

Table 9: Distribution of VAS Scores between the groups across the time intervals

Visits	Propolis	Tacrolimus	T test	P value
Baseline	6.700 ± 1.828	5.300 ± 2.359	1.483	0.155 (NS)
Active phase (end)	0.100 ± 0.316	0.000 ± 0.000	1.000	0.331 (NS)
FU1	1.500 ± 3.064	0.100 ± 0.316	1.437	0.168 (NS)
FU2	0.600 ± 1.577	0.000 ± 0.000	1.203	0.245 (NS)
FU3	0.200 ± 0.632	0.000 ± 0.000	1.000	0.331 (NS)

EFFECT OF TOPICAL MEDICATIONS ON THE CLINICAL SIGNS

The clinical signs of OLP (erythema and ulcerations) were measured using a semi-quantitative scale, Modified Oral Mucositis Index (MOMI). To make the results less cumbersome, the respective erythema scores during each visit of the active phase were summed up and the total score at the end of active phase was obtained for each patient. Table 10 & 11. depict cumulative scores of all the 10 patients at baseline, end of active phase and follow ups (FU1, FU2, FU3).

A.) ERYTHEMA

PROPOLIS (Group A)

Baseline visit

At the baseline, the scores for each site were summed up and a total score of higher value was obtained. In all 10 patients, severity of erythema was noted with a mean value of 1.700 ± 0.948 (Table 10).

Active Phase (1st visit to 4th visit)

At the end of active phase, out of the 10 patients, 2 (20%) patients had a score of 1 each (mild erythema). Rest all had a score of 0 (no erythema). The mean value at the end of active phase was 0.200 ± 0.421 (Table 10). A significant reduction was noted in the severity of erythema.

1st Follow Up

On 1st follow up i.e. after 1 month of end of active phase, out of 10 patients, 2 (20%) patients regained erythematous areas due to recurrence of the lesions with a score of 2 (moderate erythema), 1 (10%) patient had a cumulative score of 5, rest 6 (60%) patients had a score of 0 (no erythema). 1 (10%) patient did not turn up. The mean value on 1st follow up was 0.600 ± 1.074 (Table 10).

2nd Follow Up

On 2nd follow up i.e. after 1 month of 1st follow up, out of 10 patients, 1 (10%) patient had a score of 1 (mild erythema) and other with a cumulative score of 4, rest 6 (60%) patients had a score of 0 (no erythema). 2 (20%) patients did not turn up. The mean value on 2nd follow up was 0.300 ± 0.674 (Table 10).

3rd Follow Up

On 3rd follow up i.e. after 1 month of 2nd follow up, out of 10 patients, 1 (10%) patient had a score of 1 (mild erythema) and other with a cumulative score of 3, rest 6 (60%) patients had a score of 0 (no erythema). 2 (20%) patients did not turn up. No statistical significant difference was observed. The mean value on 3rd follow up was also 0.300 ± 0.674 (Table 10).

TACROLIMUS (Group B)

Baseline visit

At the baseline, the scores for each site were summed up and a total score of higher value was obtained. In all 10 patients, severity of erythema was noted with a mean value of 1.100 + 0.875 (Table 10).

Active Phase (1st visit to 4th visit)

At the end of active phase, out of the 10 patients, all the patients (100%) had a score of 0 (no erythema). The mean value at the end of active phase was 0.000 ± 0.000 (Table 10). A significant reduction was noted in the severity of erythema.

1st Follow Up

On 1st follow up i.e. after 1 month of end of active phase, all the patients (100%) had a score of 0 (no erythema). The mean value at the end of active phase was 0.000 ± 0.000 (Table 10).

2nd Follow Up

On 2nd follow up i.e. after 1 month of 1st follow up, out of 10 patients, 9 (90%) patients had a score of 0 (no erythema). 1 (10%) patients did not turn up. The mean value at the end of active phase was 0.000 ± 0.000 (Table 10).

3rd Follow Up

On 3rd follow up i.e. after 1 month of 2nd follow up, out of 10 patients, 8 (80%) patients had a score of 0 (no erythema). 2 (20%) patients did not turn up. The mean value at the end of active phase was 0.000 ± 0.000 (Table 10).

Table 10: Distribution of Erythema Scores between the groups across time intervals

Visits	Propolis	Tacrolimus	T test	P value
Baseline	1.700 ± 0.948	1.100 + 0.875	1.470	0.159 (NS)
Active phase (end)	0.200 ± 0.421	0.000 ± 0.000	1.500	0.151 (NS)
FU1	0.600 ± 1.074	0.000 ± 0.000	1.765	0.095 (NS)
FU2	0.300 ± 0.674	0.000 ± 0.000	1.406	0.177 (NS)
FU3	0.300 ± 0.674	0.000 ± 0.000	1.406	0.177 (NS)

** = Highly Significant; * = Significant; NS = Nothing Significant

GROUPS COMPARISON

Student-t test was applied to find differences in erythema scores between Propolis and Tacrolimus groups. On comparing erythema scores between Propolis and Tacrolimus groups, no significant difference was found between the time intervals. However, significant difference was noted at the end of active phase and follows ups, with Tacrolimus (mean = 0.000 ± 0.000) showing better results then Propolis. In toto, erythema decreased from baseline to follow up (third month) from a mean of 1.700 ± 0.948 reducing to 0.300 ± 0.674 in the Propolis group and a reduction from 1.100 + 0.875 to 0.000 ± 0.000 in the Tacrolimus group.

Observation:

Between both the groups, Tacrolimus showed a better response in reducing the severity of erythema, compared to Propolis. There was statistically significant (p = 0.000) improvement in the erythema scores.

B.) ULCERATIONS

PROPOLIS (Group A)

Baseline visit

At the baseline, out of the 10 patients, in only 1 patient ulceration was noted with a score of 2 (between 0.25-1 cm^2). Rest all the 9 (90%) patients had a score of 0 (no ulcerations). The mean value of 0.200 ± 0.632 (Table 11).

Active Phase (1st visit to 4th visit)

At the end of active phase, out of the 10 patients, all the patients (100%) had a score of 0 (no ulcerations). The mean value at the end of active phase was 0.000 ± 0.000 (Table 11). The ulcerations had completely healed showing significant improvement.

1st – 3rd Month Follow Ups

All the patients (100%) had a score of 0 (no ulcerations). The mean value on 1st follow up was 0.000 ± 0.000 (Table 11).

TACROLIMUS (Group B)

From the baseline visit till the third month follow up, all the 10 patients (100%) had a score of 0 (no ulcerations). The mean value across all the time intervals was was 0.000 ± 0.000 (Table 11).

GROUPS COMPARISON

Student-t test was applied to find differences in ulceration scores between Propolis and Tacrolimus groups. Ulcers were found only in the Propolis group, however, statistical significant difference was noted at the end of active phase (0.000 ± 0.000) from baseline (0.200 ± 0.632). No significant difference was noted between the groups for ulceration scores between Propolis and Tacrolimus groups, with a *p* value of 0.331. Table 11. shows distribution of ulceration scores between both the groups across the time intervals.

Table 11: Distribution of Ulceration Scores between the groups across time intervals

Visits	Propolis	Tacrolimus	T test	P value
Baseline	0.200 ± 0.632	0.000 ± 0.000	1.000	0.331 (NS)
Active phase (end)	0.000 ± 0.000	0.000 ± 0.000	-	-
FU1	0.000 ± 0.000	0.000 ± 0.000	-	-
FU2	0.000 ± 0.000	0.000 ± 0.000	-	-
FU3	0.000 ± 0.000	0.000 ± 0.000	-	-

PRESENCE OF PIGMENTATION ASSOCIATED WITH THE LESION

Presence of pigmentation in OLP lesions is an indication of postinflammatory changes and repeated occurence and healing of the previous lesions.

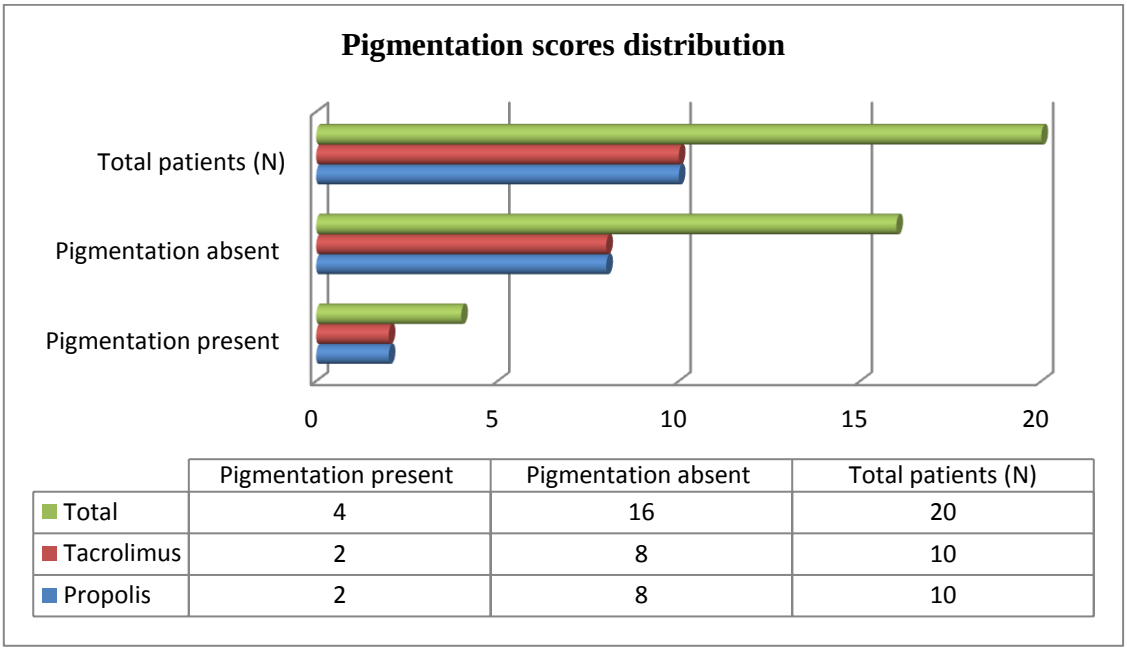
At the baseline visit, in both the groups no statistically significant differences were noted for pigmentation score distribution among the groups.

PROPOLIS (Group A)

At the baseline, out of all the 10 patients, 2 (20%) patients had a score of 1 (pigmentation present) , while 8 (80%) patients had a score of 0 (pigmentation absent) (Graph 5).

TACROLIMUS (Group B)

At the baseline, out of all the 10 patients, 2 (20%) patients had a score of 1 (pigmentation present) , while 8 (80%) patients had a score of 0 (pigmentation absent) (Graph 5).



	Pigmentation present	Pigmentation absent	Total patients (N)
Total	4	16	20
Tacrolimus	2	8	10
Propolis	2	8	10

Graph 5: Distribution of Pigmentation Scores between groups across time intervals

RECURRENCE OF THE LESIONS

OLP lesions have recurrent property. Recurrence of the lesions were observed in few cases after the end of active phase of the medication.

PROPOLIS (Group A)

1st Follow Up

On 1st follow up i.e. after 1 month of end of active phase, out of 10 patients, 3 (30%) patients had a score of 1 (recurrence present), 6 (60%) patients had a score of 0 (no recurrence). 1 (10%) patient did not turn up. The mean value on 1st follow up was 0.300 $\pm$ 0.483 (Table 12).

2nd Follow Up

On 2nd follow up i.e. after 1 month of 1st follow up, out of 10 patients, 8 (80%) patients had a score of 0 (no recurrence). 2 (20%) patients did not turn up. There was significant improvement as the recurrent lesions had exhibited resolution.The mean value on 2nd follow up was 0.000 ± 0.000 (Table 12).

3rd Follow Up

On 3rd follow up i.e. after 1 month of 2nd follow up, out of 10 patients, 8 (80%) patients had a score of 0 (no recurrence). 2 (20%) patients did not turn up. No recuurence of the lesions was observed. The mean value on 3rd follow up was 0.000 ± 0.000 (Table 12).

TACROLIMUS (Group B)

1st Follow Up

On 1st follow up i.e. after 1 month of end of active phase, out of 10 patients, 1 (10%) patient had a score of 1 (recurrence present), while rest 9 (90%) patients had a score of 0 (no recurrence). The mean value on 1st follow up was 0.100 ± 0.316 (Table 12).

2nd Follow Up

On 2nd follow up i.e. after 1 month of 1st follow up, out of 10 patients, 2 (20%) patients had a score of 1 (recurrence present), 7 (70%) patients had a score of 0 (no recurrence). 1 (10%) patient did not turn up. The patient who had recurrence in the 1st follow up exhibited resolution of the lesion. The mean value on 2nd follow up was 0.200 ± 0.421 (Table 12).

3rd Follow Up

On 3rd follow up i.e. after 1 month of 2nd follow up, out of 10 patients, 8 (80%) patients had a score of 0 (no recurrence). 2 (20%) patients did not turn up. No recurrence was observed. The recurrent lesions exhibited resolution. The mean value on 3rd follow up was 0.000 ± 0.000 (Table 12).

GROUPS COMPARISON

Student t-test was applied to draw comparison of the recurrence scores between the groups. The recurrence of the lesions was found to be non significant in the first month with a *p* value of 0.288. Tacrolimus group demonstrated slightly higher recurrence in the second month, in comparison to the Propolis group with no recurrence, however it was found to be non significant in the second month with a *p* value of 0.151. In the third month, both the groups showed no recurrence. Table 12. demonstrates distribution of Recurrence Scores between the groups across the time intervals.

Table 12: Distribution of Recurrence Scores between the groups across the time intervals

Recurrence (Follow-Ups)	Propolis	Tacrolimus	T test	P value
FU1	0.300 ± 0.483	0.100 ± 0.316	1.095	0.288 (NS)
FU2	0.000 ± 0.000	0.200 ± 0.421	1.500	0.151 (NS)
FU3	0.000 ± 0.000	0.000 ± 0.000	-	-

OVERALL PERFORMANCE OF PROPOLIS AND TACROLIMUS

Comparing overall performance of both the groups, Group A (Propolis) and Group B (Tacrolimus) in the management of symptomatic Oral Lichen Planus, both showed equal efficacy. No significant statistical differences were observed. However, Tacrolimus resulted in a quicker response in symptom reduction. Both the medications were well tolerated by the patients, with no side effects observed. To achieve complete resolution of the lesions, the gel application course should be duly followed, as done by majority of the patients in this study. According to the results drawn, it can be stated that both the medications exhibit good effectiveness in OLP management and can be utilised in future too.

DISCUSSION

LP is a chronic autoimmune, mucocutaneous, inflammatory disease of unspecified etiology. As the etiopathogenesis of OLP is dubious, the failure to achieve complete appropriate treatment may be the reason for its delayed regression and frequent recurrence. The first line of treatment for OLP is corticosteroids, but owing to their adverse effects, alternative therapeutics are being tried out.[7]

The involvement of the immune system as a primary factor in the pathogenesis of LP has been recently established. T-cell activation is principal to the pathogenesis of LP. Basal cell layer debasement, a band-like infiltration of T lymphocytes and macrophages are seen. A third "T helper" subdivision has been recognized which plays a key role in defense against extracellular pathogens by rendering immune and inflammatory responses through secretion of cytokines like Interleukin 17. It is a potent stimulator for recalling, activating, and immigrating neutrophils; and producing INF-alpha, IL-B from macrophages by increasing the expression of factors for chemokines, MMPs, and IL-6. [25,61] Stress being a triggering factor of this condition, as reported by Chaudhary S (2004) [80]; EL. Tawil, Sediki and Hassan [81] (2009) and Kalkur, Sattur and Guttal [82] (2015) .Majority of the study participants also reported stress in their history associated with various issues like financial, studies, household work, job, loss of a family member, systemic illness, etc. These factors prove to be a significant contributor in the disease initiation and progression.

Keeping in mind the above (especially the management protocol, as nowadays people have an inclination and better acceptability towards herbal medications and tacrolimus is a better alternative to conventional steroids due to their adverse effects), this study was designed to evaluate the efficacy of topical propolis and topical tacrolimus in the management of symptomatic OLP and to further strengthen the previously obtained results in few studies conducted. We hypothesize that propolis (a natural product with great potential in treating oral lesions) and tacrolimus (already established mechanism of blockage of calcineurin function) by minimizing the levels of IL-17 could reduce the underlying inflammatory mechanism and thereby preventing the lymphocytic activity causing the basement membrane destruction. This hypothesis is also supported by Zenouz TA *et al.* [223] in which they proved that propolis administration significantly decreased IL-17 serum levels.

Recently, the use of natural products, such as *Propolis*, has gained considerable interest. It is a sticky, resinous substance collected by honey bees from the sap, leaves, and buds of plants mixed with secreted beeswax. It has found to be used extensively in Ayurvedic medicine for centuries. It is rich in different biological properties with significant therapeutic benefits offering antioxidant, anti-inflammatory, antibacterial, antiviral, antifungal, anti-tumor, and immuno-modulatory effects.[15]

These properties have prompted curious researchers to evaluate its efficacy on various oral lesions and conditions chiefly, oral lichen planus, oral candidiasis, recurrent aphthous stomatitis, radiation mucositis, denture stomatitis, herpes labialis, etc.[214-220] In this study the antioxidant, anti-inflammatory properties and possible immunomodulatory (though it is mainly assessed when systemic absorption occurs) of propolis were considered. The results of our study are comparable to the studies conducted by Joshy *et al.* [133] and Zyada *et al.* [222] They, too, evaluated the efficacy of Propolis (mucoadhesive gel form) in the management of OLP. They also proved Propolis to be a promising pharmacological agent for inhibiting epithelial cell proliferation and anti-inflammatory effects, and immunomodulatory effects.

20 patients fulfilling the inclusion criteria participated in this randomized controlled trial. The demographic pattern of the study participants with OLP was also recorded in this study. According to this study, the patients were between 18-65 years old, and their mean age was 34.7 years in Group A (propolis) and 35.4 years in Group B (tacrolimus). The prevalence of OLP was found to be in the younger age group, which was similar to the mean age reported by Munde *et al.* [44] and lower than the mean age reported by Xue *et al.* [43] , Chitturi *et al.* [45], Tak *et al.* [116] and Joshy *et al.* [133]. This variation might be due to the difference in ethnicity and geographic locations. The mean age group reported by Xue *et al.* [36] , Munde *et al.* [44], Chitturi *et al.* [45], Tak *et al.* [116] and Joshy *et al.* [133] were 52 years, 36.9 years, 45.72 years, 43 years and 45.3 years, respectively.

Many studies assert that OLP is more predominant in females as they have been more prone to stress and hormonal imbalance. However, in this study, an apparent male preference (70% males and 30% females) was observed in both the groups A and B, which might be due to the small sample size compared to other studies. Similar observations were noted in studies conducted by Munde *et al.* [44], where M:F ratio was 1.61:1, by Sachdev *et al.* [59], males (75.4%) and Keshari *et al.* [115] where M:F ratio was 1.45:1. The results were in contrast to Joshy *et al.* [133], where the M:F ratio was found 1:1, and Scully and El-Kom [22]**,** Mohan *et al.* [41], Silvermann *et al.* [56] and Varghese *et al.*[57] ,where a clear female predominance was seen.

Patients with clinically diagnosed symptomatic OLP were enrolled in the study, based on the modified WHO clinical diagnostic criteria (2003), proposed by Van der Meiji *et al.* [132] This criteria was also used by Munde *et al.* [44] , Chitturi *et al.* [45] and Joshy *et al.* [133] in their studies. No cutaneous lesions were found in the study participants. OLP lesions occurring alone range from 0.5% to 2.2% as reported by Edwards and Kelsch [110]; and Eisen D. [111] In this study, there was an unequal distribution among all the OLP variants exhibiting symptoms. Only two patients had an erosive form of OLP, whereas atrophic form was more prevalent either alone or in conjunction with a reticular pattern which was dominant throughout. Though the reticular variant is asymptomatic, in this study,

patients experienced burning sensation with clinical presentation of the reticular pattern too. Not to forget that this subtype is most likely to transform into erosive variant associated with burning sensation, as mentioned by Scully *et al.* [18] and Silvermann *et al.* [56] In studies carried out by Munde *et al.* [44] and Chitturi *et al.* [45] reticular type was the most common pattern, followed by erosive and atrophic forms. Similar dominance of atrophic pattern was observed in the study conducted by Joshy A *et al.* [133]

The most common site where OLP lesions occurred in our study was in the buccal mucosa (with few lesions extending onto the retromolar area), followed by the gingiva, tongue, and labial mucosa. On the buccal mucosa mostly the lesions had bilateral presentation similar to report by Silvermann *et al.* [56]. Our findings were in accordance with the studies by Munde *et al.* [44] , Tak *et al.* [116] and Joshy A *et al.* [133] where the most common site also was the buccal mucosa, followed by gingiva. Hoever, in this study, three patients uniquely had a unilateral presentation of OLP on the buccal mucosa, similar to a case reported Bajpai M *et al.* [112] Studies have reported that more than one mucosal surface can be involved which is in accordance with our study observations, wherein a combination of gingival and buccal mucosal lesions existed. 4 patients also revealed pigmented areas mostly with reticular pattern. This subtype is chronic and linked with hyperpigmentation due to repeated occurrence and prolonged healing course of the previous lesions. Chitturi *et al.* [45] also observed hyperpigmentation in their maximum patients. Pigmentation associated with OLP lesions in the study participants has not been accounted by Joshy *et al.* [133] Gupta PC *et al.* [194] observed 11% of the lesions seen in Ernakulam developed pigmentation.

To assess the clinical signs and symptoms 2 scales (VAS and MOMI) were used in the present study. Their relevance is properly discussed by Chainani W *et al.* [123] in their review**.** These scales are predominantly used for assessment of symptomatic oral lesions. The two groups i.e. Group A (propolis) and Group B (tacrolimus) had 10 patients each who were evaluated for the burning sensation and erythema at baseline (1st visit), active phase (7^{th} ,14^{th}, 21^{st}, 28^{th} day), and follow up phase (of 3 months). Clinically, the VAS scores and the lesion size reduced in patients with symptomatic OLP. In the present study, an evident decline was observed in the VAS scores and clinical symptoms with the adequate application of topical propolis gel 5% and topical tacrolimus gel 0.1%, proving effective topical remedies. In the present study, the patients in both the groups, i.e., Group A (Propolis) and Group B (tacrolimus), reported a significant reduction in the intensity of burning sensation from the baseline till the follow-up period. Among ten patients in Group A, nine patients reported complete resolution of erythema at the end of the active phase, with only one patient, had a VAS score of 1. However, in 3 patients on the first follow-up, due to recurrence of the lesions, the burning sensation had returned. Two patients had complete remission at the end of their

follow-up period, with only one patient showing a significant but not complete reduction. Among ten patients in Group B, all the patients reported complete resolution of erythema at the end of the active phase. However, in 1 patient on the first follow-up, due to recurrence of the lesions, the burning sensation had returned but had complete remission at the end of the follow-up period. An intragroup analysis showed a significant reduction in the VAS scores in each group, but the intergroup analysis didn't show any significant differences in the time interval. However, the tacrolimus group showed a quicker response in comparison to the propolis group.

All the patients reported a significant reduction in the severity of erythema from the baseline to the follow-up period. On comparing erythema scores between Propolis and Tacrolimus groups, no significant difference was found between the time intervals. Among ten patients in Group A, seven patients reported complete resolution of erythema at the end of the active phase, with two patients, had mild erythema. However, in 3 patients on the first follow-up, due to recurrence of the lesions, the erythema had returned. However, it significantly reduced gradually on its own till the third follow-up. Among ten patients in Group B, all the patients reported complete resolution of erythema from the baseline till the end of follow-up. There was a statistically significant improvement in the erythema scores in both the groups, with tacrolimus showing a better response in reducing the severity of erythema compared to Propolis. Ulcers were found only in 1 patient of the Propolis group. However, a statistically significant difference was noted at the active phase from baseline (patient did not come for the follow-up). No such significant difference was noted between the groups for ulceration scores.

Constratingly, Joshy *et al.* [133] used NRS for pain assessment scale and compared topical application of Propolis with triamcinolobe acetonide among 27 patients diagnosed with symptomatic OLP, out of which 15 patients were in the control group and the rest 12 were in the study group. The patients in the control group received triamcinolone acetonide 0.1% while the patients in the study group received propolis gel. Both the groups were evaluated for pain and erythema at baseline (1st visit), first follow‑up (7th day), and second follow‑up (14th day) using NRS and MOMI. The patients in both the groups showed a statistically significant reduction in the pain and erythema scores from baseline to second follow‑up visit. However, on comparison of the reduction in pain and erythema scores between the two groups, the difference was found to be statistically insignificant.

OLP possesses recurrent property, being chronic in nature. It is linked with prolonged stress. In our study, recurrence of the lesions was observed in few cases after the end of an active phase of the medication. In Group A, out of 10 patients, three patients showed recurrence in the first follow-up. The lesions showed significant or complete resolution of the recurrent lesions in the subsequent

follow-ups. In Group B patients, out of 10 patients, one patient showed recurrence in the first follow-up, while two patients showed recurrence in the second follow-up. However, the lesions showed significant or complete resolution of the recurrent lesions in the third follow-up. Group comparison revealed the recurrence of the lesions to be non-significant in the first and second months. Tacrolimus group demonstrated slightly higher recurrence in the second month in comparison to the Propolis group. 2 patients in each group were inconsistent during their follow-up period. Either further assessment could not be done, or telephonic conversation was established in their cases.

No significant literature is available concerning the association of recurrence of OLP lesions, post Propolis therapy. However, few OLP patients have shown flare-ups soon after stopping the tacrolimus treatment. Similar to this study, recurrence was also observed in the clinical trials and studies conducted by Rozycki *et al.* [140] (who reported recurrence within 1 to 2 weeks of cessation of tacrolimus therapy); Laeijendecker *et al.* (2006) [143] also reported recurrence in his study patients and Gupta PC *et al.* [194] also found recurrence of OLP lesions in his patients over a period of 10 years. This is in contrast to Shichinohe R. *et al*. (2005) [141] who reported of no recurrence. Recurrence of OLP in the study participants has not been accounted by Joshy *et al.* [133]

All the study participants exhibited significant improvement on topical application of Propolis and tacrolimus, which is the strength of this study. According to our study, Propolis is comparative in its efficacy to tacrolimus. Swarna *et al.* [138] and Laeijendecker *et al.* [143] reported that tacrolimus was more effective than topical corticosteroids (triamcinolone and clobetasol) in controlling painful symptoms of erosive OLP. Therefore, it can be speculated that both Propolis and tacrolimus can be used as alternative medications to conventional corticosteroids, having minimal to no localized adverse effects, as also reported by Joshy *et al.* [133] (found propolis equally efficacious as corticosteroids). Zydaa *et al.*[222] also proved that propolis is a promising pharmacological agent in the mangement of OLP.

People usually are allergic to Propolis on external contact with the skin or mucous membrane rather than oral administration. [224] Therefore, it must be enunciated that topical Propolis does not accord any adverse effects in the oral cavity, unlike topical corticosteroids. No adverse effects were reported with the use of topical Propolis in this study participants. Topical application of tacrolimus has been reported as safe with few adverse effects. No significant adverse effects were reported with the use of topical tacrolimus in our study participants. However, out of 10 patients in the tacrolimus group, 5 patients exhibited slight mucosal staining which faded with time and was almost or completely absent on their follow-ups; but only 1 patient showed persistence till the 3rd follow-up. Mucosal staining has also been reported by Fricain *et al*. (2005) [151] in his patient. Other common side effects on application of topical tacrolimus include mucosal burning sensation (which may be caused by the

vehicle, not to the drug itself), sore throat, transient dysgeusia, headache, etc. as reported by Rozycki *et al.* [140] ,Lozada-Nur and Sroussi [142] ,Laeijendecker *et al.* (2006) [143] ,Hodgson *et al.* (2003) [144] ,Thomson *et al.* (2004) [145] ,Byrd *et al.* (2004) [146] ,Vente *et al.* (1999) [149] ,Kaliakatsou *et al.* (2002) [150] and Corrocher *et al.*(2008) [147] in their patients. None of these were reported in this study participants. However, all the reported adverse effects cease as the treatment continues and as the symptomatic lesions heal with time. Of note, only one patient experienced a minor aphthous ulcer during the follow-up period in the tacrolimus group, but it healed completely.

STUDY LIMITATIONS

The small sample size was found to be a significant limitation of this study. Larger sample size would have allowed for a compelling statistical analysis. Another limitation of the study was the dependence on patient compliance during the follow-up period, which could not be monitored. Also, since the patients were followed up only for three months, the recurrence rate of OLP could not be elicited for a more extended period. A longer follow-up period (6-12 months to few years) will help demonstrate a difference in the recurrence rate of OLP among the comparative medication groups

FUTURE RECOMMENDATIONS

Various clinical trials have been conducted using tacrolimus, which now has established a role in OLP treatment. However, the role of Propolis has not been ascertained entirely. In our knowledge no literature is available pertaining to the evaluation of the efficacy of these two medications in the mangement of OLP and this is the first study to do so. Future studies can be conducted using a larger sample size to authenticate further the effectiveness of Propolis alone or establish a comparison with tacrolimus (like this study) or any other medication, in the management/treatment of OLP.

CONCLUSION

- This study aimed to compare and evaluate the efficacy of 5% topical Propolis and 0.1% topical Tacrolimus gels in management of OLP, which was successfully met. The current study comprised of 20 patients diagnosed with OLP, among which 10 patients each were in both the groups i.e Group A and Group B. The patients in Group A received 5% topical propolis while the patients in Group B received 0.1% topical Tacrolimus. Both the groups were evaluated for clinical symptoms (burning sensation, erythema, ulceration) and lesion presentation at the baseline visit, at the end of active phase (end of 1 month) and 3 follow-ups at the interval of one month each.
- The following conclusions were drawn:

  Objectives considering the evaluation of individual potency of both the medications were met, as Propolis and tacrolimus individually were effective in resolving the burning sensation and the lesions, in each patient. Other objective was to do a comparative evaluation of both the topical applications in order to assess the one with better efficacy in the management of OLP. The 5% topical Propolis was found to be as effective as 0.1% topical Tacrolimus in the management of OLP. It exhibits anti-inflammatory, anti-oxidant, and immunomodulatory effects, which may significantly reflect in its clinical efficiency. The application of topical propolis at the prescribed dose i.e. 5% was also found to be effective with no adverse reactions. Similarly, no serious adverse reactions were noted with the use topical tacrolimus and it was also found to be effective at the prescribed dose i.e. 0.1% tacrolimus. However, clinically 1 patient experienced occurrence of a minor aphthous ulcer during application of topical tacrolimus, but since it exhibits anti-inflammatory and possible localised immunomodulatory action, it helped in regression of the same.
- Another objective of the study was to check for any recurrences in both the groups. Each patient was evaluated for the same and accordingly assessed. All patients exhibiting recurrence, with their partial and/or complete resolution was noted in the subsequent follow-ups.
- This study confirms the equivalent clinical efficacy, safety of application, well tolerability with quick onset of effects of topical Propolis and topical Tacrolimus in their respective concentrations. Hence we conclude that our results provided empirical hints for the better management of OLP.

- Considering the chronicity of the disease, and the need for the long-term treatment modalities, both tacrolimus and propolis can be proposed as a better treatment modality for OLP, especially for lesions not responding or are resistant to corticosteroids (accompanied with common adverse side effects). However, the medications used in this study do not pose any threat, with minimalistic adverse effects (in higher concentration or due to injudicious use). In the light of these results, the use of tacrolimus is efficient in the control of lesions and the symptoms associated with the OLP. Studies with a larger number of participants must be conducted to establish the use of this wonder medication at different stages of OLP.
- Natural products are nowadays preferred over synthetic formulations. Here comes the role of Propolis, which is a versatile drug and its great therapeutic potential has been widely reasearched throughout the world. It is abundant in India but still unknown to a considerable part of the population. It remains stable and free of contamination over six months of storage, is cheap and easily utilised for medicinal preparation. Considering the safety, wide obtainability and cost effectiveness, Propolis can be considered as a novel therapeutic modality in the management of OLP, alternative to conventional medications or less effective therapies. Propolis as an active pharmaceutical ingredient in topical medications for the treatment of OLP can be considered. However, further research with a larger sample size is required for a full evaluation of the efficacy of propolis. The expected participation and sample size in this study could not be achieved. This can be exempted in futuristic studies.

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ANNEXURES

ANNEXURE-1
CASE HISTORY PROFORMA
A COMPARATIVE EVALUATION OF THE EFFICACY BETWEEN TOPICAL APPLICATIONS OF PROPOLIS AND TACROLIMUS IN MANAGEMENT OF SYMPTOMATIC ORAL LICHEN PLANUS PATIENTS

DEPARTMENT OF ORAL MEDICINE & RADIOLOGY
BabuBanarasi Das College of Dental Sciences, Lucknow (U.P.)

OPD NO: Case No:

Name: Age: Sex:

Marital status: Occupation:

Address:

Contact No:

CHIEF COMPLAINT:

HISTORY OF PRESENT ILLNESS:

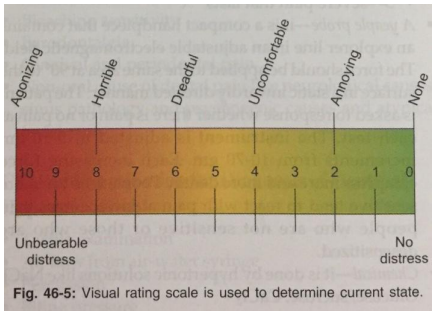


Fig. 46-5: Visual rating scale is used to determine current state.

DURATION
>1 year
1-5 years
5-10 years
>10 years

PAST MEDICAL HISTORY:

DRUG ALLERGY:

PAST DENTAL HISTORY:

INTRAORAL SOFT TISSUE EXAMINATION:

SITE	**ERYTHEMA** *MOMI INDEX **0 = normal 1 = mild erythema 2 = moderate erythema 3 = severe erythema**	**ULCERATION(SIZE)** *MOMI INDEX **0 = no ulcerations 1 = between 0 and 0.25 cm^2 2 = between 0.25 and 1 cm^2 3 = ≥1 cm^2**	**PATTERN**
LIPS			
LABIAL MUCOSA			
BUCCAL MUCOSA			
VESTIBULE			
TONGUE			
FLOOR OF THE MOUTH			
HARD AND SOFT PALATE			
FAUCIAL PILLARS			

PROVISIONAL DIAGNOSIS:

TREATMENT PLAN:

PATIENT ASSESSMENT:

ACTIVE PHASE

1ST VISIT

BURNING SENSATION (VAS)	**SITE**	**ERYTHEMA**	**ULCERATION**

2ND VISIT

BURNING SENSATION (VAS)	**SITE**	**ERYTHEMA**	**ULCERATION**

3RD VISIT

BURNING SENSATION (VAS)	**SITE**	**ERYTHEMA**	**ULCERATION**

4TH VISIT

BURNING SENSATION (VAS)	**SITE**	**ERYTHEMA**	**ULCERATION**

FOLLOW-UP PHASE

1ST MONTH

BURNING SENSATION (VAS)	**SITE**	**ERYTHEMA**	**ULCERATION**

2ND MONTH

BURNING SENSATION (VAS)	**SITE**	**ERYTHEMA**	**ULCERATION**

3RD MONTH

BURNING SENSATION (VAS)	**SITE**	**ERYTHEMA**	**ULCERATION**

SIGNATURE OF STUDENT SIGNATURE OF GUIDE

ANNEXURE -2
CONSENT FORM

Title of the study…….

Study Number…….

Subject's Full Name……

Date of Birth/Age……

Address of the Subject……

Phone No. and email address……..

Qualification……

Occupation: Student/Self employed/Service/Housewife/Other

1. I confirm that I have read and understood the Participant Information Document dated ……. for the above study and have had the opportunity to ask questions

   OR

   I have been explained the nature of the study by the investigator and had the opportunity to ask questions.
2. I understand that my participation in the study is voluntary and given with the free will without any duress and that I am free to withdraw at any time, without given any reason and without my medical care or legal rights being affected.
3. I understand that the sponsor of the project, others working on the sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trail. However, I understand that my identity will not be revealed in any information released to third parties or published.
4. I agree not to restrict the use any data or results that arise from this study provided such a use is only for scientific purpose(s).

5. I agree to participate in the above study for the future research

   Yes [ ] No [ ] Not Applicable [ ]
6. I have been explained about the study, and have fully understood them. I have also read and understand the participant/volunteer's information document given to me.

   Signature/Thumb impression of the subject/Legally acceptable Representative……....

   Signatory's Name…….....Date…….....

Signature of Investigator's Name……..……..…

Study Investigator's Name……...Date……..

Signature of the witness……..…

Name of witness……...Date……..

Received a signed copy of the duly filled consent form

Signature/Thump Impression of the subject/Legally acceptable representative…….Date……

ANNEXURE -2

सहमति पत्र

अध्ययन का शीर्षक.....

अध्ययन संख्या.....

विषय का पूरा नाम.....

जन्म / आयु की तिथि.....

विषय का पता.....

फोन नंबर और ईमेल पता.....

योग्यता.....

व्यवसाय: छात्र / स्वयं नियोजित / सेवा / गृहिणी / अन्य

1. मैं पुष्टि करता हूं कि मैंने प्रतिभागी सूचना दस्तावेज को पढ़ और समझ लिया है .....उपर्युक्त अध्ययन के लिए और प्रश्न पूछने का अवसर मिला है

या

मुझे जांचकर्ता द्वारा अध्ययन की प्रकृति की व्याख्या की गई है और मुझे प्रश्न पूछने का अवसर मिला है।

2. मैं समझता हूं कि अध्ययन में मेरी भागीदारी स्वैच्छिक है और किसी भी दुविधा के बिना मुफ्त इच्छा के साथ दी गई है और मैं किसी भी समय बिना किसी कारण के और बिना चिकित्सा देखभाल या कानूनी अधिकारों के प्रभावित किए बिना वापस लेने के लिए स्वतंत्र हूं।

3. मैं समझता हूं कि परियोजना के प्रायोजक, प्रायोजक की तरफ से काम करने वाले अन्य लोग, नैतिकता समिति और नियामक प्राधिकरणों को वर्तमान अध्ययन के संबंध में और मेरे आगे के किसी भी शोध के संबंध में मेरे स्वास्थ्य रिकॉर्ड देखने की अनुमति की आवश्यकता नहीं होगी इसके संबंध में आयोजित किया गया, भले ही मैं निशान से पीछे हट जाऊं। हालांकि, मैं समझता हूं कि मेरी पहचान तीसरे पक्ष को जारी या प्रकाशित किसी भी जानकारी में प्रकट नहीं होगी।

4. मैं इस अध्ययन से उत्पन्न होने वाले किसी भी डेटा या परिणामों के उपयोग को प्रतिबंधित नहीं करने के लिए सहमत हूं बशर्ते ऐसा उपयोग केवल वैज्ञानिक उद्देश्यों के लिए है।

5. मैं भविष्य के शोध के लिए उपर्युक्त अध्ययन में भाग लेने के लिए सहमत हूं

हां [] नहीं [] लागू नहीं []

6. मुझे अध्ययन के बारे में समझाया गया है, और उन्हें पूरी तरह से समझ लिया है। मैंने मुझे दिए गए प्रतिभागी / स्वयंसेवक के सूचना दस्तावेज को भी पढ़ और समझ लिया है।

विषय / कानूनी रूप से स्वीकार्य के हस्ताक्षर / अंगूठे की छाप

प्रतिनिधि.....

हस्ताक्षरकर्ता का नाम.....

जांचकर्ता के नाम का हस्ताक्षर.....

अध्ययन जांचकर्ता का नाम .... दिनांक.....

गवाह का हस्ताक्षर.....

गवाह का नाम ..... दिनांक .....

विधिवत भरे सहमति फॉर्म की एक हस्ताक्षरित प्रति प्राप्त की
विषय / कानूनी रूप से स्वीकार्य प्रतिनिधि के हस्ताक्षर / अंगूठे का निशान..... दिनांक .....

ANNEXURE- 3
ETHICAL APPROVAL FORM

BABU BANARASI DAS COLLEGE OF DENTAL SCIENCES
(FACULTY OF BBD UNIVERSITY), LUCKNOW

INSTITUTIONAL RESEARCH COMMITTEE APPROVAL

The project titled **"A Comparative Evaluation of the Efficacy Between Topical Applications of Propolis and Tacrolimus in Management of Symptomatic Oral Lichen Planus Patients."** submitted by **Dr Areeba Shahid** Post graduate student from the **Department of Oral Medicine & Radiology** as part of MDS Curriculum for the academic year 2018-2021 with the accompanying proforma was reviewed by the Institutional Research Committee present on **27th November 2018** at BBDCODS.

The Committee has granted approval on the scientific content of the project. The proposal may now be reviewed by the Institutional Ethics Committee for granting ethical approval.

Prof. Vandana A Pant
Co-Chairperson

Prof. B. Rajkumar
Chairperson

ANNEXURE-4

Babu Banarasi Das University
Babu Banarasi Das College of Dental Sciences,
BBD City, Faizabad Road, Lucknow – 226028 (INDIA)

Dr. Lakshmi Bala
Professor and Head Biochemistry and
Member-Secretary, Institutional Ethics Committee

Communication of the Decision of the VIIth Institutional Ethics Sub-Committee

IEC Code: 08 **BBDCODS/01/2019**

Title of the Project: A Comparative Evaluation of the Efficacy Between Topical Applications of Propolis and Tacrolimus in Management of Symptomatic Oral Lichen Planus Patients.

Principal Investigator: Dr. Areeba Shahid **Department:** Oral Medicine & Radiology

Name and Address of the Institution: BBD College of Dental Sciences Lucknow.

Type of Submission: New, MDS Project Protocol

Dear Dr. Areeba Shahid,

The Institutional Ethics Sub-Committee meeting comprising following four members was held on 10th January 2019.

1.	Dr. Lakshmi Bala Member Secretary	Prof. and Head, Department of Biochemistry, BBDCODS, Lucknow
2.	Dr. Amrit Tandan Member	Prof. & Head, Department of Prosthodontics and Crown & Bridge, BBDCODS, Lucknow
3.	Dr. Rana Pratap Maurya Member	Reader, Department of Orthodontics & Dentofacial Orthopedics, BBDCODS, Lucknow
4.	Dr. Sumalatha M.N. Member	Reader, Department of Oral Medicine & Radiology, BBDCODS, Lucknow

The committee reviewed and discussed your submitted documents of the current MDS Project Protocol in the meeting.
The comments were communicated to PI thereafter it was revised.

Decisions: The committee approved the above protocol from ethics point of view.

Forwarded by:

Lakshmi Bala 22/01/19

(Dr. Lakshmi Bala)
Member-Secretary
IEC

Member-Secretary
Institutional Ethic Committee
BBD College of Dental Sciences
BBD University
Faizabad Road, Lucknow-226028

(Dr. B. Rajkumar)
Principal
BBDCODS

PRINCIPAL
Babu Banarasi Das College of Dental Sciences
(Babu Banarasi Das University)
BBD City, Faizabad Road, Lucknow-226028

ANNEXURE-5
MASTER CHART

VAS Scores

Case No.	Med Group	OPD NO.	Age	Gender	Baseline	AP1	AP2	AP3	AP4	FU1	FU2	FU3
1	Propolis	35890	65	Male	9	5	1	0	0	5	1	0
2	Tacrolimus	36643	50	Female	4	2	1	0	0	0	0	0
3	Propolis	36645	45	Female	6	4	1	0	0	0	0	0
4	Tacrolimus	40710	20	Male	2	1	0	0	0	0	0	0
5	Tacrolimus	43335	46	Male	10	8	5	1	0	1	0	0
6	Tacrolimus	42640	45	Female	5	5	3	1	0	0	0	0
7	Tacrolimus	46610	28	Male	6	2	1	0	0	0	0	0
8	Propolis	48986	21	Female	7	5	8	3	0	0	0	0
9	Propolis	60720	21	Male	5	4	2	1	0	1	0	0
10	Tacrolimus	20600	45	Female	5	4	3	3	0	0	0	0
11	Propolis	63385	39	Female	5	9	8	1	0	9	5	2
12	Tacrolimus	9565	23	Male	6	3	1	0	0	0	0	0
13	Propolis	69315	30	Male	7	6	4	1	0	0	0	0
14	Propolis	75615	40	Male	7	2	1	0	0	0	0	0
15	Propolis	79450	29	Male	4	5	5	1	0	0	-	-
16	Tacrolimus	1145	25	Male	3	1	0	0	0	0	0	0
17	Tacrolimus	6002	50	Male	8	5	3	1	0	0	-	-
18	Tacrolimus	6865	22	Male	4	2	0	0	0	0	0	-
19	Propolis	8985	20	Male	7	5	3	1	0	0	0	0
20	Propolis	6900	37	Male	10	8	5	4	1	-	-	-

ERYTHEMA Scores

Case No.	Med Group	OPD NO.	Age	Gender	Baseline	AP1	AP2	AP3	AP4	FU1	FU2	FU3
1	Propolis	35890	65	Male	4	1	1	0	0	2	0	0
2	Tacrolimus	36643	50	Female	1	1	0	0	0	0	0	0
3	Propolis	36645	45	Female	3	1	0	0	0	0	0	0
4	Tacrolimus	40710	20	Male	2	1	0	0	0	0	0	0
5	Tacrolimus	43335	46	Male	5	1	0	0	0	0	0	0
6	Tacrolimus	42640	45	Female	0	0	0	0	0	0	0	0
7	Tacrolimus	46610	28	Male	2	1	1	0	0	0	0	0
8	Propolis	48986	21	Female	4	2	2	1	0	0	0	0
9	Propolis	60720	21	Male	2	1	1	1	0	2	1	1
10	Tacrolimus	20600	45	Female	0	0	0	0	0	0	0	0
11	Propolis	63385	39	Female	2	1	2	2	1	5	4	3
12	Tacrolimus	9565	23	Male	1	0	0	0	0	0	0	0
13	Propolis	69315	30	Male	4	2	2	2	1	0	0	0
14	Propolis	75615	40	Male	0	0	0	0	0	0	0	0
15	Propolis	79450	29	Male	2	1	2	0	0	0	-	-
16	Tacrolimus	1145	25	Male	1	1	0	0	0	0	0	0
17	Tacrolimus	6002	50	Male	6	2	1	0	0	0	-	-
18	Tacrolimus	6865	22	Male	1	1	1	0	0	0	0	-
19	Propolis	8985	20	Male	2	1	1	0	0	0	0	0
20	Propolis	6900	37	Male	7	2	1	0	0	-	-	-

ULCERATION Scores

Case No.	Med Group	OPD NO.	Age	Gender	Baseline	AP1	AP2	AP3	AP4	FU1	FU2	FU3
1	Propolis	35890	65	Male	0	0	0	0	0	0	0	0
2	Tacrolimus	36643	50	Female	0	0	0	0	0	0	0	0
3	Propolis	36645	45	Female	0	0	0	0	0	0	0	0
4	Tacrolimus	40710	20	Male	0	0	0	0	0	0	0	0
5	Tacrolimus	43335	46	Male	0	0	0	0	0	0	0	0
6	Tacrolimus	42640	45	Female	0	0	0	0	0	0	0	0
7	Tacrolimus	46610	28	Male	0	0	0	0	0	0	0	0
8	Propolis	48986	21	Female	0	0	0	0	0	0	0	0
9	Propolis	60720	21	Male	0	0	0	0	0	0	0	0
10	Tacrolimus	20600	45	Female	2	0	0	0	0	0	0	0
11	Propolis	63385	39	Female	0	0	0	0	0	0	0	0
12	Tacrolimus	9565	23	Male	0	0	0	0	0	0	0	0
13	Propolis	69315	30	Male	0	0	0	0	0	0	0	0
14	Propolis	75615	40	Male	0	0	0	0	0	0	0	0
15	Propolis	79450	29	Male	0	0	0	0	0	0	-	-
16	Tacrolimus	1145	25	Male	0	0	0	0	0	0	0	0
17	Tacrolimus	6002	50	Male	0	0	0	0	0	0	-	-
18	Tacrolimus	6865	22	Male	0	0	0	0	0	0	0	-
19	Propolis	8985	20	Male	0	0	0	0	0	0	0	0
20	Propolis	6900	37	Male	2	2	0	0	0	-	-	-

PATTERN & PIGMENTATION

Case No.	Med Group	OPD NO.	Age	Gender	Duration	Site	Pattern	Pigm (P= 1, A=0)
1	Propolis	35890	65	Male	4 to 5 years	Rt. & Lt. BM, Max. G irt 23,24,25	R + A	1
2	Tacrolimus	36643	50	Female	3 to 4 years	Lt. BM	R + Pq	0
3	Propolis	36645	45	Female	1 to 1.5 years	Lo. LM, Lt. BM	R + A	0
4	Tacrolimus	40710	20	Male	8 to 9 mo	Rt. & Lt. BM	R	0
5	Tacrolimus	43335	46	Male	7 mo	Rt. & Lt. BM, RA, AM	R + A	0
6	Tacrolimus	42640	45	Female	2 years	Rt. & Lt. BM	Pq + R	1
7	Tacrolimus	46610	28	Male	9 to 10 mo	Lo. LM, Rt. & Lt. BM	R + Pq	0
8	Propolis	48986	21	Female	2 mo	Rt. & Lt. BM, T	A + R + P	0
9	Propolis	60720	21	Male	1 year	Max. G, Max. LM, Max. V	A + R	0
10	Tacrolimus	20600	45	Female	3 to 4 mo	Rt. & Lt. BM	R	1
11	Propolis	63385	39	Female	2 to 3 years	Rt. & Lt. BM	An + R	0
12	Tacrolimus	9565	23	Male	2 years	Rt. BM	R	0
13	Propolis	69315	30	Male	3 to 4 years	Rt. & Lt. BM, RA	R + A	0
14	Propolis	75615	40	Male	7 to 8 mo	T	P	1
15	Propolis	79450	29	Male	2 mo	Rt. & Lt. BM, RA	R + P	0
16	Tacrolimus	1145	25	Male	4 to 5 mo	T	Pq	0
17	Tacrolimus	6002	50	Male	2 years	Rt. & Lt. BM	A + R	0
18	Tacrolimus	6865	22	Male	4 mo	Rt. & Lt. BM, Max. G irt anteriors	R + An + P	0
19	Propolis	8985	20	Male	4 to 5 mo	Rt. & Lt. BM	R	0
20	Propolis	6900	37	Male	1 to 2 years	Rt. & Lt. BM, RA, PR	E + A + Pq	0

RECURRENCE

Case No.	Med Group	OPD NO.	Age	Gender	FU1 (P= 1, A = 0)	FU2	FU3
1	Propolis	35890	65	Male	1	0	0
2	Tacrolimus	36643	50	Female	0	0	0
3	Propolis	36645	45	Female	0	0	0
4	Tacrolimus	40710	20	Male	0	1	0
5	Tacrolimus	43335	46	Male	0	0	0
6	Tacrolimus	42640	45	Female	1	0	0
7	Tacrolimus	46610	28	Male	0	0	0
8	Propolis	48986	21	Female	0	0	0
9	Propolis	60720	21	Male	1	0	0
10	Tacrolimus	20600	45	Female	0	0	0
11	Propolis	63385	39	Female	1	0	0
12	Tacrolimus	9565	23	Male	0	0	0
13	Propolis	69315	30	Male	0	0	0
14	Propolis	75615	40	Male	0	0	0
15	Propolis	79450	29	Male	0	-	-
16	Tacrolimus	1145	25	Male	0	0	0
17	Tacrolimus	6002	50	Male	0	-	-
18	Tacrolimus	6865	22	Male	0	1	-
19	Propolis	8985	20	Male	0	0	0
20	Propolis	6900	37	Male	-	-	-

ANNEXURE- 6
STATISTICAL ANALYSIS FORMULAS

Arithmetic Mean

The most widely used measure of central tendency is arithmetic mean, usually referred to simply as the mean, calculated as

$$\bar{X} = \frac{\sum_{i=1}^{n} X_i}{n}$$

Standard deviation and standard error

The standard deviation (SD) is the positive square root of the variance, and calculated as

$$SD = \sqrt{\frac{\sum_{i=1}^{n} X_i}{SD}}$$

where, n= no. of observations. The and SE (standard error of the mean) is calculated as

$$SE = \frac{SD}{\sqrt{n}}$$

Minimum and Maximum

Minimum and maximum are the minimum and maximum values respectively in the measure data and range may be dented as below

Range = Min to Max

and also evaluated by subtracting minimum value from maximum value as below

Range = Maximum value-Minimum value

Median

The median is generally defined as the middle measurement in an ordered set of data. That is, there are just as many observations larger than the median as there are smaller. The median (M) of a sample of data may be found by third arranging the measurements in order of magnitude (preferably ascending). For even and odd number of measurements, the median is evaluated as

$$M = [(n+1)/2]^{th} \text{ observation- odd number}$$

$$M = [n(n+1)/2]^{th} \text{ observation – even number}$$

Student's t Test

Student's t-test was used to calculate the differences between the means of two groups

$$t = \frac{\bar{X}_1 - \bar{X}_2}{SE}$$

$$\sum X_i \qquad 2 \qquad \sqrt{\frac{n}{(\sum X_4)} \left(\frac{SD}{1} \right) SE = \frac{}{n}}$$

S^2 is the pooled variance and n_1 and n_2 are number of observations in group 1 and 2 respectively. The degrees of freedom (DF) is calculated as

$$DF = n1 + n2 - 2$$

Chi-square test

The chi-square (χ^2) test is used to compare the categorical data as

$$\chi^2 = \Sigma\Sigma \frac{(Fij - fij)^2}{fij}$$

where, Fij is the observed frequency while fij the expected frequency. The degrees of freedom (DF) is calculated as

$$DF= (r-1)\ (c-1)$$

Analysis of Variance

Analysis of variance (ANOVA) is used when we compare more than two groups simultaneously. The purpose of one-way ANOVA is to find out whether data from several groups have a common mean. That is, to determine whether the groups are actually different in the measured characteristic. One way ANOVA is a simple special case of the linear model. For more than two independent groups, simple parametric ANOVA is used when variables under consideration follows Continuous exercise group distribution and groups variances are homogeneous otherwise non parametric alternative Kruskal-Wallis (H) ANOVA by ranks is used. The one way ANOVA form of the model is

$$Y_{ij} = \alpha_{.j} + \varepsilon_{ij}$$

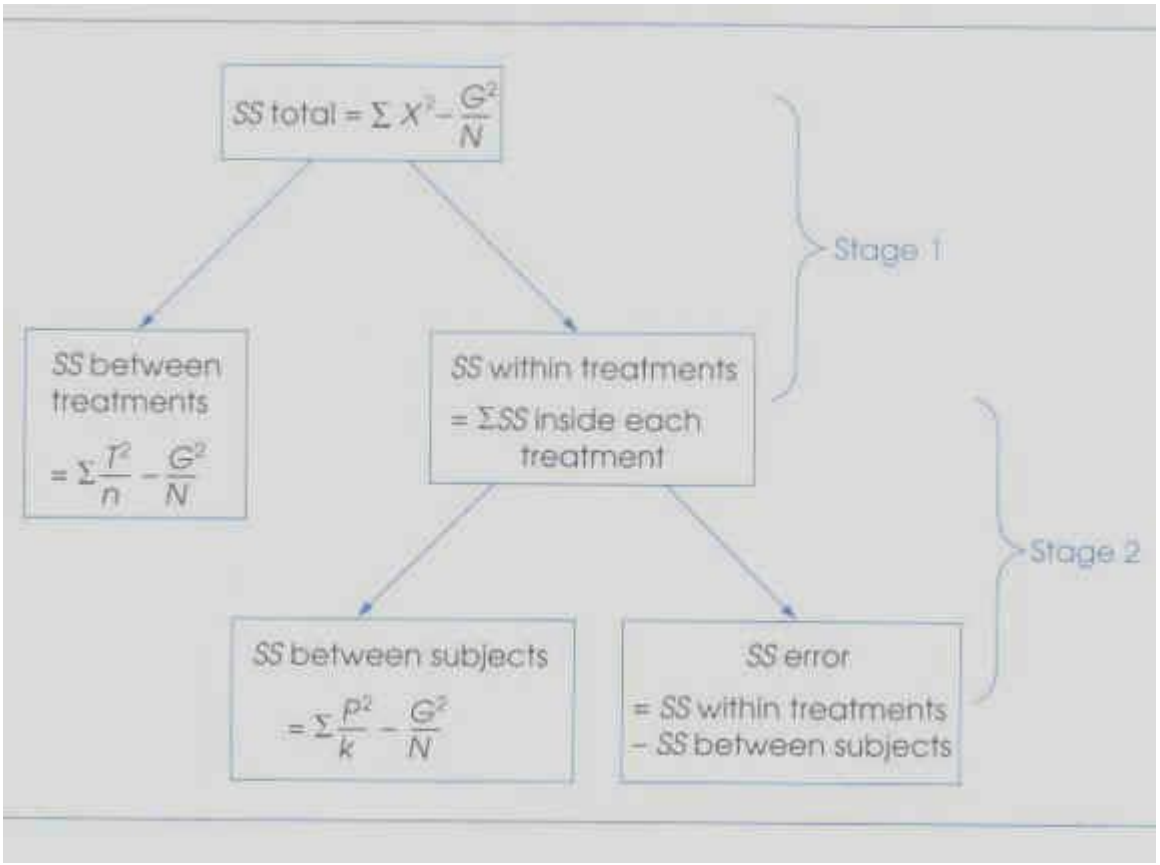
where;

- Y_{ij} is a matrix of observations in which each column represents a different group.
- $\alpha_{.j}$ is a matrix whose columns are the group means (the "dot j" notation means that α applies to all rows of the j^{th} column i.e. the value α_{ij} is the same for all i).
- ε_{ij} is a matrix of random disturbances.

The model posits that the columns of Y are a constant plus a random disturbance. We want to know if the constants are all the same.

Repeated measures ANOVA:

Repeated measures ANOVA is used to find significant differences between multiple measures of the same variable taken on the same or matched subjects either under different conditions or over two or more time period.



The first stage of the repeated-measures ANOVA uses the same notation and formulas as the between-subjects ANOVA. In the first stage, total variability is divided into variability between treatments and variability within treatments.

The second stage we remove individual differences from the within treatment variability, making for a smaller, more precise estimate of error . The remaining variability in the denominator is called residual variance or error variance because it measures how much variance is expected just by chance after the individual differences have been removed.

k = number of treatments

n = number of scores in each treatment

N = total number of scores in the entire study

G = grand total of all scores in the experiment

T = the sum of the scores in each treatment condition

P = the total of scores for each participant (participant totals)

Statistical significance

Level of significance "*P*" is the probability signifies level of significance. The mentioned P in the text indicates the following:

$P > 0.05$ - not significant (ns)

$P < 0.05$ - just significant (*)

$P < 0.01$ - moderate significant (**)

$P < 0.001$ - highly significant (***)

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