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University of Misan

College of Dentistry

Title

Role of Autoimmunity in the Incidence of Oral Lichen Planus: Systematic Review

A graduation project submitted to the College of Dentistry in partial fulfillment of the requirements for the degree of Bachelor of Dental Science.

Supervisor:

Lect. Dr. Ahmed Mohammed Alwan

Students:

Um al-Banen Nasser Resn

Zainab Hassan Abdullah

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

صدق الله العلي العظيم

(سورة يونس – الآية 10)

Dedication

To the one who is life itself... To you, my mother, the source of warmth, safety, and unwavering strength. To the great man... To you, my father, whom God has graced with dignity and wisdom, who taught me to give without expecting, and whose name I carry with pride.

To all those who acted, then passed away... yet live on forever. To those whose impact remains eternal.

To my respected professors, who enriched me with their knowledge and were guiding lights along my path— my deepest gratitude to you

Acknowledgments

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I am deeply grateful to my family, especially my parents, for their unconditional love, patience, and support. Their belief in me has been my greatest strength.

Thank you all.

Certification of supervision

I hereby certify that the project entitled "**Role of autoimmunity in the incidence of oral lichen planus: systematic review**" was conducted by fifth-year students under my supervision at the University of Misan, College of Dentistry, in partial fulfillment of the requirements for the degree of Bachelor of Science in Dentistry.

Supervisor name: lect. Dr. Ahmed Mohammed Alwan

Signature:

Date:

Defense Committee Certification

We, the undersigned, certify that we have read and evaluated the graduation project entitled: **"Role of autoimmunity in the incidence of oral lichen planus: systematic review"** submitted by the fifth-year students of the **College of Dentistry / University of Misan**.

Having examined the content and findings of the project and observed the oral defense, we approve the project as fulfilling the partial requirements for the **degree of Bachelor of Science in Dentistry**.

Committee Members:

1. Dr.

Chairperson

Signature: _____ Date: _____

2. Dr.

Member

Signature: _____ Date: _____

3. Dr.

Member

Signature: _____ Date: _____

Dean's Certification

I hereby certify that the graduation project entitled: **“Role of autoimmunity in the incidence of oral lichen planus: systematic review”** submitted by fifth-year students of the **College of Dentistry / University of Misan**, has been reviewed and approved by the examining committee.

The project fulfills the academic requirements for the degree of **Bachelor of Science in Dentistry**.

Dean of the College of Dentistry

Prof. Dr. Ridha Alwan Hassan

Signature: _____

Date: _____

Abstract

Introduction

Oral Lichen Planus (OLP) is a chronic inflammatory condition of the oral mucosa characterized by immune dysregulation and multifactorial etiology. This study explores the theoretical basis of immune-mediated mechanisms and microbial interactions contributing to OLP pathogenesis.

Method

A literature-based qualitative approach was used, focusing on peer-reviewed data concerning cytokine activity, immune cell dynamics, and psychological associations. No clinical or laboratory experiments were conducted in this research.

Result

The findings suggest a prominent role for proinflammatory cytokines and specific microbial species in perpetuating the chronicity of OLP. Additionally, psychological stress appears to have a potential impact on the recurrence and intensity of symptoms.

Conclusion

The data highlights the complexity of immune and microbial interplay in OLP and emphasizes the need for integrative therapeutic strategies. Future directions may benefit from exploring non-conventional treatments targeting both biological and psychological factors.

Keywords: Oral Lichen Planus, immune response, cytokines, microbial involvement, regenerative therapy.

List of abbreviations

No.	Abbreviation	Full Term
1.	MHC	Major Histocompatibility Complex
2.	ROS	Reactive Oxygen Species
3.	LPS	Lipopolysaccharide
4.	BMZ	Basement Membrane Zone
5.	PDT	Photodynamic Therapy
6.	LLLT	Low-Level Laser Therapy
7.	PBM	Photobiomodulation
8.	NAVS	Naphthalan (mineral oil used in therapy)
9.	HA	Hyaluronic Acid
10.	TA	Triamcinolone Acetonide (topical corticosteroid)
11.	PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
12.	MeSH	Medical Subject Headings
13.	NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
14.	JAK/STAT	Janus Kinase / Signal Transducer and Activator of Transcription
15.	TLR	Toll-like Receptor
16.	DIF	Direct Immunofluorescence
17.	CASP	Critical Appraisal Skills Programme

18.	HCV	Hepatitis C Virus
19.	HSV	Herpes Simplex Virus
20.	HIV	Human Immunodeficiency Virus
21.	CBC	Complete Blood Count
22.	MHC	Major Histocompatibility Complex
23.	ROS	Reactive Oxygen Species
24.	LPS	Lipopolysaccharide
25.	BMZ	Basement Membrane Zone
26.	PDT	Photodynamic Therapy
27.	LLLT	Low-Level Laser Therapy
28.	PBM	Photobiomodulation
29.	NAVS	Naphthalan (mineral oil used in therapy)
30.	HA	Hyaluronic Acid
31.	TA	Triamcinolone Acetonide (topical corticosteroid)
32.	Th1	T helper type 1 cells
33.	Th2	T helper type 2 cells
34.	Th17	T helper type 17 cells
35.	Treg	Regulatory T cells
36.	HHV-7	Human Herpesvirus 7
37.	EMT	Epithelial-Mesenchymal Transition
38.	AZA	Azathioprine

39.	Se	Selenium

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Chapter one

Introduction

1. Chapter one

1.1. Introduction

The immune system interfaces with the external environment of individual groups and others and then filters out elements that are identified as non-self. It is a highly combative defense system capable of eliminating viruses, bacteria, germs and other particles that only harm the health of the organism. From the physiological side, the body's immune system response is a program alien to the network of communications between cells, molecules and cells of cells (1).

Oral manifestations are often the first signs of autoimmune diseases , making dentists important in early detection and diagnosis. This can lead to early recognition of these signs, which can have a significant impact on patients' lives. The most prominent of these autoimmune diseases are systemic lupus erythematosus, Sjogren's syndrome, fundus lupus, and Behcet's disease. The mucosa is often the primary site of signs and symptoms of this need.(2)(4).

Cellular Mechanisms of Autoimmunity , Self-tolerance in T-lymphocytes is maintained through three key mechanisms: deletion, anergy, and suppression. Deletion, or central tolerance, occurs in the thymus, where autoreactive T-cells are eliminated through apoptosis. A second round of elimination happens in the thymic medulla, ensuring further removal of self-reactive T-cells. This process is regulated by interactions between Fas and Fas ligand. Disruptions in these pathways, such as defects in Fas/FasL, result in the persistence of autoreactive T-cells and the development of systemic autoimmunity. Understanding these cellular mechanisms is essential for developing targeted therapeutic strategies for autoimmune diseases (5).

Cytokines and chemokines are small protein molecules secreted by cells and expressed on immune cells. These molecules provide an essential part of the differentiation and migration of immune cells, but they are directed towards

specific immune cell subtypes. Given that recent studies have shown that some cytokines and chemokines that support many, such as IFN-γ, WIL-2, CCL2, and CXCL12, may also act as anti-mediators, this opens up the prospect of their use as short-term drugs. At the same time, only distinct mediators, such as TGF-β, may in certain cases, in combination with other cytokines, show distinct positive effects and contribute to the polarized CD4+ Th17 cells that contribute to beneficial benefits.

It is important to clarify that the specific function of pro-and anti-cytokines depends on three main factors: the local concentration of the cytokine, the stage of the disease at the time of its administration, and its interaction with other cytokines (3).

Cytokines are vital factors that play a key role in regulating innate and adaptive immune responses. Dysregulation of their production may lead to the development of diseases such as immunodeficiency, allergy, or autoimmune disorders, making them an important component in the mechanisms of many immune-mediated inflammatory diseases , Studies have revealed abnormal expression patterns of a group of inflammatory cytokines, including IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-17, IL-18, TGF-β, IFN-γ, and TNF-α in lesional tissues, saliva, serum, and peripheral blood mononuclear cells of OLP patients. These patterns suggest a dysregulation of the immune system, highlighting the role of cytokines as key factors in the pathogenesis of this disease (7).

Lichen planus (LP), Lichen planus (LP), a term derived from the Greek “leichen” (tree moss) and the Latin “planus” (flat), was first described by Erasmus Wilson in 1869. as a chronic disease affecting the skin, scalp, nails, and mucosa. While LP is often a benign condition, it carries a rare risk of malignant transformation. Oral lichen planus (OLP), a subtype, was linked to carcinoma for the first time by François Henri Hallopeau (8-9).

Mucosal immune disease where a complex set of immune events is believed to initiate or perpetuate this condition (11-10).

The primary cause is unknown, as it sometimes occurs as a reaction to a drug or contact with a metal and is often feared, when the cause is removed. It is classified as chronic and thus varies in the severity of its symptoms from asymptomatic to very severe symptoms. Diagnosis of this disease represents a difficult challenge for doctors in general and dentists in particular due to its great similarity from the clinical and histological aspects to lichenoid drug reaction lichenoid mucositis and lichenoid dermatitis, . It appears in three different forms (Reticular which is the most common and is asymptomatic and in different locations in the oral cavity, Erosive which is similar to desqumative gingivitis and its severity ranges from a mild burning sensation to severe pain, Erythematous) (12).

The prevalence of lichen planus ranges from 0.9% to 1.2% of the general population, and does not exceed 2% in adults. It most often affects middle-aged people, with the average age at diagnosis being 50–55 years. However, cases have been reported in all age groups, including children younger than 7 years (according to unpublished data). Studies show that women are more likely to have lichen planus than men, with females accounting for about 67% of cases. Familial cases of lichen planus are rare, with only about 100 cases reported in the scientific literature, and it is thought that some may be coincidental, especially since some members of affected families show atypical clinical manifestations (13).

Oral lichen planus (OLP) is an autoimmune disorder in which T cells, particularly CD8+ T cells, play a major role in the pathogenesis of the disease. Both mast cells and CD8+ T cells within the epithelium contribute to the pathogenesis, as these cells are present at sites of basement membrane damage in this disorder. The interaction between mast cells and T cells is thought to

contribute to the continued development of OLP lesions, as this interaction is thought to facilitate the migration of T cells from the blood vessels into the epithelium and stratum propria, resulting in the breakdown of the extracellular matrix. In this disease, multiple inflammatory mediators, such as chymase, tumor necrosis factor alpha (TNF-α), and tryptase, are released as a result of mast cell lysis. Upon lysis of these cells, TNF-α is released, which stimulates T cells to increase the secretion of RANTES, a protein that contributes to the recruitment of more immune cells. In addition, activated T cells within the lesions secrete matrix metalloproteinase (MMPs), which degrade the basement membrane and promote lesion progression (14).

To diagnose OLP, doctors first look for these visible signs during an oral exam. However, because OLP can look like other oral conditions, a biopsy is usually needed.

During the biopsy, a small piece of tissue is taken and examined under a microscope. Typical findings include inflammation under the surface of the tissue, damage to the lower layer of cells, and a specific pattern in the tissue structure. Special tests, like immunohistochemistry, can also help differentiate OLP from other conditions like oral cancer or similar lesions.

While the risk of OLP turning into cancer is low, it can happen, especially with erosive or ulcerated forms. Regular check-ups are recommended to monitor any changes. Recent research highlights the importance of combining clinical observation, tissue analysis, and advanced lab techniques to ensure an accurate diagnosis and proper management (15).

The treatment of oral lichen planus should be individualized based on the severity and extent of the disease. A multidisciplinary approach, including medical management, patient education, and regular follow-up, is crucial for effective disease control and prevention of complications.

Topical corticosteroids are commonly used to manage OLP due to their anti-inflammatory properties. A comparative study with long-term follow-up indicated that both systemic and topical corticosteroids are effective in treating OLP, with topical applications being preferred for localized lesions (16).

Chemotherapeutic Agents Explored for OLP: Methotrexate:

1. Mechanism: Methotrexate is an immunosuppressive agent that inhibits DNA synthesis, thereby reducing inflammation.
2. Azathioprine: Azathioprine is an immunosuppressive medication that inhibits purine synthesis, leading to reduced lymphocyte proliferation (17).
3. Excisional Surgery: Surgical excision of localized lesions may be considered, especially when they are symptomatic and unresponsive to other treatments (18).

Sometimes traditional treatment methods may not be useful in treating OLP, so T_Cell immune modulation (mesenchymal stem cell) can be used. These cells have the ability to regenerate oral tissues damaged by this disease and can be used systemically or topically.

This hypothesis is based on some properties of these cells, including: These cells are easy to isolate from some tissues such as bone marrow and fat and multiply them in the laboratory which provides them in large quantities, the immune properties of these cells and their ability to inhibit immune responses, which helps reduce inflammation and immune problems, and also the nature of OLP disease and that it is an autoimmune disease by T cells (T cells are a type of white blood cell responsible for coordinating and regulating the immune response. In the case of OLP, T cells become overly active and begin attacking the cells lining the mouth, causing inflammation and painful ulcers.) They have the ability to inhibit the activity of T cells and reduce the excessive immune

response. This may help relieve inflammation and reduce symptoms in OLP patients. The clinical importance of treating OLP with MSC-Mediated is that it reduces the use of conventional drugs that in turn suppress immunity with long-term use (19).

Some research and its results have revealed that stem cell treatment has a guarantee as a new therapeutic approach in treating OLP (20).

Stem cells have great potential to help treat many diseases that don't have effective treatments yet. Research in this area is growing quickly. Stem cells are special because they can renew themselves, transform into different types of cells, and have the ability to become various tissues. However, there is still limited research on how stem cell therapy can be used to treat common oral conditions like oral sub mucous fibrosis, oral lichen planus, oral ulcers, and oral mucositis (21).

1.2. Aims

1. To explore the immunological mechanisms contributing to the pathogenesis of Oral Lichen Planus (OLP).

2. To analyze the interplay between microbial agents and host immune responses in OLP.

3. To examine the psychological dimensions associated with OLP and their influence on disease progression.

4. To evaluate existing therapeutic strategies for OLP and their limitations.

5. To assess the potential of future therapies such as stem cells and nanotechnology in managing OLP.

6. To contribute to the theoretical understanding of OLP as a chronic inflammatory condition with multifactorial etiology.

1.3. Objectives

1. To identify key immune cells and cytokines involved in the inflammatory response of OLP.

2. To investigate the possible role of microbial colonization in modulating immune behavior in oral tissues.

3. To highlight the psychological burden faced by patients suffering from chronic oral mucosal lesions.

4. To classify and compare current pharmacological, herbal, and non-pharmacological treatments.

5. To explore emerging therapeutic modalities through literature-based projections and theoretical evaluation.

1.4. Questions

1. What are the primary immunological pathways implicated in the initiation and persistence of OLP?

2. How do specific cytokines influence the immune microenvironment of oral mucosal tissues in OLP cases?

3. What is the hypothesized role of oral microbiota in triggering or sustaining chronic inflammation in OLP?

4. In what ways might psychological stressors exacerbate the severity or recurrence of OLP lesions?

5. How do current treatment options align with the underlying pathophysiology of OLP?

6. What are the theoretical benefits and risks associated with stem cell application in oral mucosal healing?

7. Could nanotechnology offer targeted therapeutic delivery in OLP management? If so, how?

8. How might a multi-modal treatment strategy be more effective than monotherapy in OLP cases?4-how does stem cell therapy compare to traditional treatment for OLP in effectiveness and safety?

Chapter Two

Method

2. Chapter Two: Method

2.1. Study design

This study was conducted as a systematic review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The primary objective was to comprehensively evaluate and synthesize current findings on the immunopathogenesis of Oral Lichen Planus (OLP), with a specific focus on cytokine-mediated mechanisms, immune cell dynamics, and therapeutic strategies—including both conventional and emerging treatments. The review aimed to identify molecular patterns and clinical outcomes that could support a better understanding of OLP's pathophysiology and guide evidence-based management.

2.2. Eligibility Criteria

To ensure relevance and scientific rigor, clear inclusion and exclusion criteria were applied:

2.2.1. Inclusion Criteria:

1. Original research studies involving human subjects clinically and/or histologically diagnosed with OLP.
2. Studies focusing on immune responses, cytokine involvement, T-cell activity, or histopathological characteristics of OLP.
3. Articles evaluating treatment strategies such as corticosteroids, immunosuppressants, biologics, or stem cell-based approaches.
4. Peer-reviewed publications between 2000 and 2024.

2.2.2. Exclusion Criteria:

1. Animal-based studies (unless providing significant insights into immune mechanisms relevant to human OLP).
2. Narrative reviews, editorials, opinion papers, or case reports lacking original data.

3. Articles published in languages other than English.

2.3. Information Sources

An extensive electronic search was carried out using the following scientific databases:

- PubMed
- Scopus
- Web of Science
- Google Scholar

In addition, manual screening of reference lists from the included articles was performed to identify any potentially missed relevant studies.

2.4. Search Strategy

The search strategy was built using a combination of controlled vocabulary (e.g., MeSH terms) and free-text keywords. Boolean operators (AND/OR) were utilized to optimize the retrieval of relevant articles. The primary search terms included:

1. 'Orallichenplanus'
2. -'Immunity'
3. - 'Autoimmune disease'
4. - 'Cytokines'
5. - 'Pro-inflammatory markers'
6. - 'T lymphocytes'
7. - 'CD4+', 'CD8+'
8. - 'Regulatory T cells'
9. - 'Mesenchymal stem cells'
10. - 'Immune dysregulation'
11. - 'Inflammatory mediators'
12. - 'Apoptosis'
13. - 'NF-κB signaling'

14.- 'Topical corticosteroids'

15.- 'Biologic therapy'

16.- 'Photodynamic therapy'

Filters were applied to limit the results to human studies, full-text availability, and English language, within the 2000–2024 timeframe.

2.5. Data Collection Process

The study selection followed a three-phase process:

1. Title and Abstract Screening: Two independent reviewers screened all retrieved records based on title and abstract to remove clearly irrelevant studies.
2. Full-Text Review: The remaining studies were examined in full text to confirm they met the eligibility criteria.
3. Data Extraction: A standardized data collection form was developed to systematically extract information from each eligible study. Extracted data included publication details, study design, immune-related findings, treatment modalities, and clinical outcomes.

2.6. Data Items

The following data variables were collected from each study:

1. Author(s) and year of publication
2. Study design (e.g., case-control, cohort, clinical trial)
3. Sample size and demographic information
4. Cytokines and immune markers studied (e.g., IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IFN-γ, TNF-α, TGF-β)
5. Types of immune cells involved (e.g., CD4+ T cells, CD8+ cytotoxic T cells, regulatory T cells, mast cells, dendritic cells)

6. Immunological pathways (e.g., Th1/Th2 imbalance, NF-κB activation, JAK/STAT signaling)

   - Therapeutic approaches examined (e.g., corticosteroids, calcineurin inhibitors, hydroxychloroquine, mesenchymal stem cell therapy, herbal medicine, photodynamic therapy)

   - Clinical outcome indicators (e.g., lesion resolution, relapse rate, symptom relief, adverse effects)

2.7. Quality Assessment

Each included study was critically appraised using the Critical Appraisal Skills Programme (CASP) checklist relevant to its design. The assessment considered:

1. Clarity of research aims
2. Appropriateness of methodology
3. Validity and reliability of findings
4. Risk of bias (selection, performance, detection, and reporting)
5. Relevance to the research question
6. Overall contribution to evidence on OLP immunopathogenesis and treatment.

Chapter Three

Results

3. Chapter Three: Results

3.1. Immune Mechanisms in Oral Lichen Planus

Oral Lichen Planus (OLP) is recognized as a chronic inflammatory condition with a strong immunological basis. The pathogenesis involves a complex interplay between immune cells and a wide range of signaling molecules. T cells, particularly CD8+ cytotoxic T lymphocytes, are considered central players in epithelial cell damage, mediated by various cytokines and chemokines. The disruption of immune tolerance, along with sustained antigenic stimulation, contributes to the persistence of inflammation in OLP lesions. The table below outlines key immune-related molecules implicated in the disease process and their respective roles (See Table-1).

Table 0-1: Immune Mechanisms in Oral Lichen Planus (21-27).

Molecule	Title of study	Year of publication	Role of this molecule	Authors name	References
IL_1	Evaluation of Pro inflammatory, NF-kappa B Dependent Cytokines:IL-1α,IL-6,IL- 8, and TNF-α in Tissue Specimens and Saliva of Patients with Oral Squamous Cell Carcinoma and Oral Potentially Malignant Disorders.	2020	contributesto the recruitment and activation of T-cells and other immunecellsintheoral mucosa, perpetuating the inflammatory response characteristic of OLP.	Karolina Babiuch and colleagues	(21)
IL_2	" Evaluation of interleukin-2 and tumornecrosisfactor- α levels in patients with lichen planus "	2012	activating and proliferating T cells, influencing the balance between T cell subsets, interacting with dendritic cells, and inducing the production of other cytokines. These actions contribute to the chronic inflammationandtissuedamage observedinOLP.	DUçmak	(22)

IL-4	Salivary and Serum Interferon-Gamma/Interleukin-4 Ratio in Oral Lichen Planus Patients: A Systematic Review and Meta-Analysis	2019	As a cytokine associated with Th2 cells, IL-4 plays a role in balancingimmuneresponses by enhancing Th2 differentiation and suppressing the production of Th1-related cytokines. In patients with OLP, shifts in the IFN-γ/IL-4 ratio have been noted, indicating a potential imbalance that could influence theprogression ofthedisease.	Hamid Reza Mozaffari	(23)
IL-5	Evaluation of mast cells, eosinophils, blood capillaries in orallichenplanusand oral lichenoid mucositis	2012	Theproliferationandmaturation of eosinophils, a type of white blood cell crucial for immune reactions and inflammatory processes, are influenced by specific factors.	D santhosh Reddy	(24)
IL-6	High serum level of interleukin-6islinked with dyslipidemia in oral lichen planus	2021	stimulatingandmaintainingthe viability of CD8+ cytotoxic T cells. In OLP, these activated CD8+ T cells attack basal keratinocytes, causing their programmedcelldeath .	Mihaela Paula Toader	(25)
TGF-B	Orallichen-planus-associated fibroblasts acquire myofibroblast characteristicsandsecrete pro-inflammatory cytokines in response to Porphyromonasgingivalis lipopolysaccharide stimulation	2018	triggers fibroblasts to overproduce collagen and other extracellularmatrixcomponents activation of fibroblasts and their transformation into myofibroblasts, which accelerates fibrosis and the formation of scar tissue.	Liping Wang	(26)
IFN-Y	IFN-γ enhances cell-mediatedcytotoxicity against keratinocytes viaJAK2/STAT1in lichen planus	2019	boosting antigen presentation throughtheincreasedexpression of MHC class I molecules on keratinocytes. This heightened expression makesthecellsmore vulnerable to destruction by	Shuail Shao	(27)

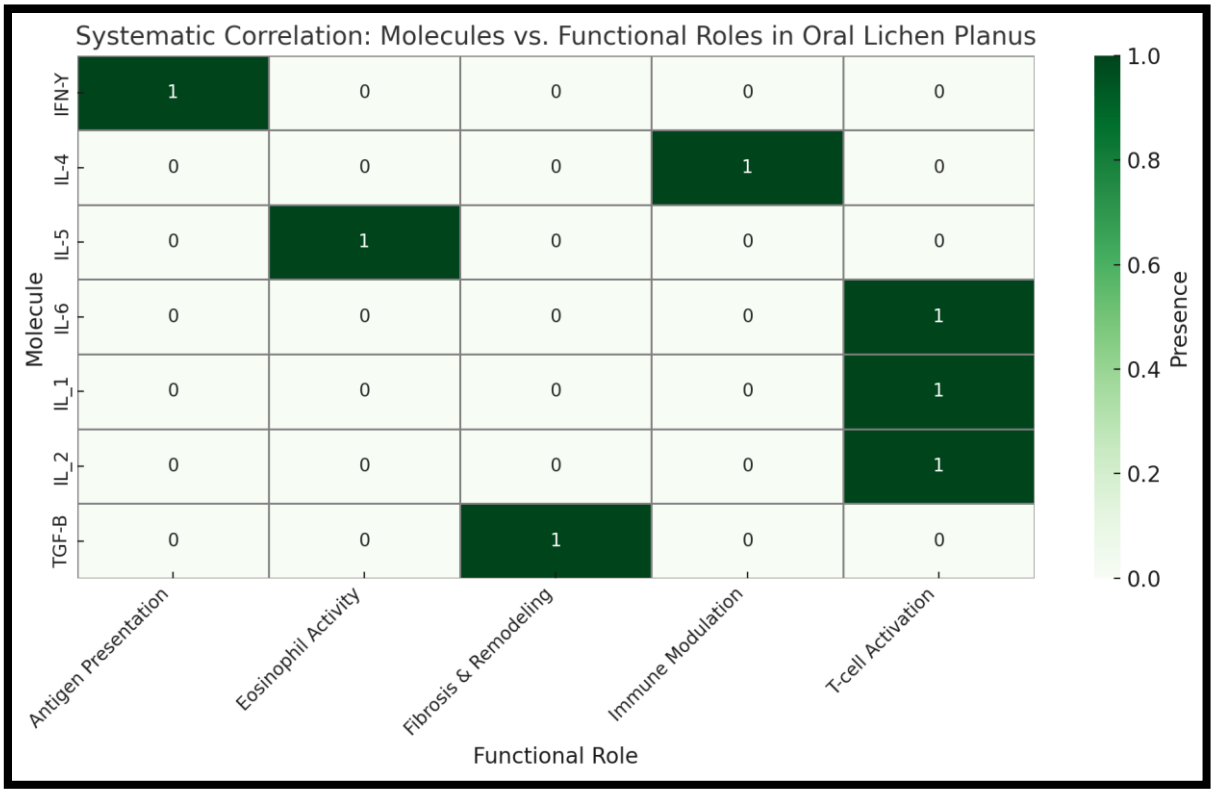

Figure 0-1: Systematic Correlation: Molecules Vs. Functional Roles In Oral Lichen Planus.

3.2. Microbial Pathogens in Oral Lichen Planus

Although Oral Lichen Planus (OLP) is mainly regarded as an autoimmune condition, growing evidence suggests that microorganisms may play a role in its initiation or progression. Specific bacteria, viruses, and fungi could serve as activating or aggravating factors by interfering with the immune response These pathogens may contribute to chronic inflammation, alter immune regulation ، and impair tissue integrity.

The table below outlines microbial agents associated with OLP and their possible mechanisms in disease pathogenesis.

Table 0-2: Microbial Pathogens in Oral Lichen Planus (29-31).

Infection	Title of study	Year of population	Roleofinfection	Authors name	Reference
Helicobacter pylori	Helicobacter pylori Infection Induces Oxidative Stress and Programmed Cell Death in Human GastricEpithelialCells	2007	Helicobacter pylori generates reactive oxygen species (ROS) and toxic substances that can injure the cells lining the oral cavity, increasing their like lihoodofundergoingprogrammed cell death (apoptosis).	Song-Ze Ding	(29)
Fusobacterium nucleatum	Pathogenic Mechanisms of Fusobacterium nucleatumonOral Epithelial Cells	2022	infiltrates connective tissues and releasesproteolyticenzymes,resulting in the breakdown of tissue integrity. Furthermore, it triggers strong inflammatory reactions by promoting the release of pro-inflammatory cytokines, potentially worsening the inflammatoryenvironment commonly associated with oral lichen planus (OLP).	Sabine Groeger	(30)
Hepatitis C Virus(HCV)	Downregulation of TLR-7 receptorinhepaticandnon-hepaticpatients with lichen planus	2012	HCV triggers changes in the antigenic componentsoftheoralmucosa,leading to the activation of cytotoxic T cells or the initiation of an antibody-mediated immune response. This results in the production of antibodies targeting the altered host structures.	AmiraEl Tawdy	(31)
Herpes SimplexVirus (HSV)	Lichen planus remission is associated with a decrease of human herpes virus type 7 protein expression in plasmacytoiddendriticcells	2007	Increased activiaion of PDCs that reinforcetothechronicinflammatory environment characteristic of OLP.	HenryJ.C.de Vries	(32)
Candida albicans (C.albicans)	A Literature Review of the RoleofCandidaalbicansin the Occurrence and Development of Several Cancers	2024	Generate nitrosamines that have the ability to activate certain pro-to-oncogenesinvolvedintheprocessof malignant transformation.	MehdiTaheri Sarvtin	(33)
Porphyromonas gingivalis	Microbiome landscape of lesionsandadjacentnormal mucosalareasinorallichen planus patient	2022	Disrupting the microbiome creates an environment where harmful bacteria can flourish, further destabilizing immunebalance‹It alsopromotesthe developmentofbiofilms,whichhinder the immune system's ability to eliminate infections, potentially extendingtheinflammatoryconditions associatedwithOLP.	JianChen	(34)

Prevotella intermedia	Periodontopathogenprofile of healthy and oral lichen planus patients with gingivitis or periodontitis	2013	not considered a direct cause of OLP butitmayexacerbatetheconditionby contributingtoinflammation,immune dysregulation, and oral microbiome imbalance.	Abdullah Seckin Ertugrul	(35)
Tannerella forsythia	Periodontopathogenprofile of healthy and oral lichen planus patients with gingivitis or periodontitis	2013	Alongsideotherharmfulbacteriain the gums, these pathogens can leadto oral dysbiosis, which refers to a disruption in the natural balance of the oral microbiome. In individuals with OLP, this imbalance may intensify the immune system's reaction, potentially causing symptoms to become more severe.	Abdullah Seckin Ertugrul	(36)
S. sanguinis	Microbiome landscape of lesionsandadjacentnormal mucosalareasinorallichen planus patient	2022	S. sanguinis is typically beneficial, maintaining oral microbiome balance bycurbingpathogenicbacteria growth. However, oral dysbiosis, marked by a riseinharmfulbacteriaandadecline in beneficial ones like S. sanguinis, can fuel inflammation, potentially worseningcondit ionslikeOLP.	JianChen	(37)
Escherichia coli	Characterization of intratissue bacterial communitiesandisolation of Escherichia coli from oral lichen planus lesions	2020	disruptthenormalimmuneresponse, contributing to the persistence and severity of OLP.	Keumjin Baek	(38)
C. glabrata	Comparative evaluation of prevalence and phenotypic variations of Candida species in patients of oral lichen planus and oral lichenoid lesions with healthy individuals - A prospectivemicrobiological study	2022	resistancetoantifungaltherapyand causes secondary infections	Priyadarshani R Sarkate	(39)
C. tropicalis	Comparative evaluation of prevalence and phenotypic variations of Candida species in patients of oral lichen planus and oral lichenoid lesions with healthy individuals - A prospectivemicrobiological study	2022	Secondaryinflationandworseningthe inflammatoryresponse.	Priyadarshani R Sarkate	(39)

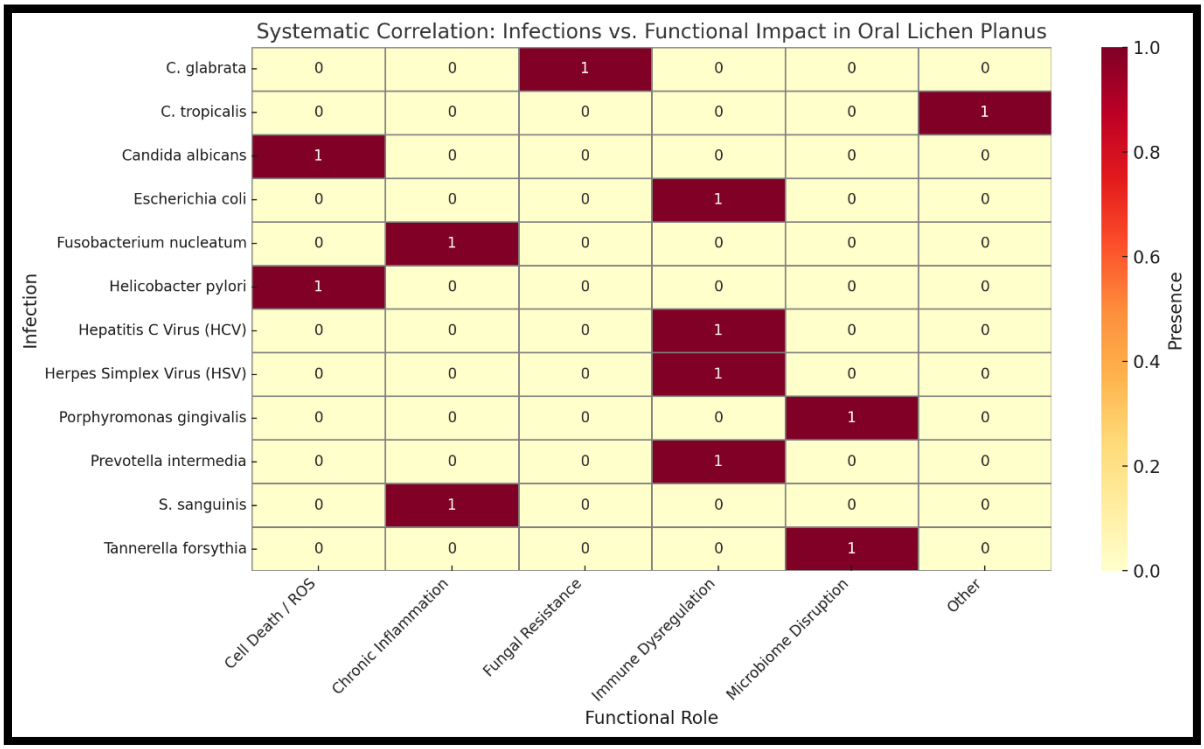

Figure 0-2: Systematic Correlation: Infections Vs. Functional Impact In Oral Lichen Planus.

3.3. Diagnostic Evaluation in Oral Lichen Planus

The diagnosis of Oral Lichen Planus (OLP) requires a systematic approach, integrating clinical assessment with confirmatory investigations. Due to its similar presentation to other mucosal disorders, a stepwise diagnostic strategy is crucial for accurate identification. Histopathological examination serves as the primary diagnostic tool, while supplementary methods—such as direct immunofluorescence (DIF), tissue biopsy, and serological testing help confirm the diagnosis and exclude mimicking condition

The following table summarizes the key diagnostic tests for OLP and their clinical utility.

Table 0-3: Diagnostic Evaluation in Oral Lichen Planus (40-43).

Tests	Titalof study	Year of public ation	Target material	Author s name	Reference

Biopsytest	Diagnosis and managementoforal lichen planus – Review	2021	OralEpithelium(Stratified Squamous Epithelium)،BasementMembraneZone (BMZ)،Subepithelial Connective Tissue .	N Gururaj	(40)
Direct Immunofl u orescence (DIF)test	Direct Immunofluorescence inOralLichenPlanus	2015	Fibrinogen , Immunoglobulins(IgG,Ig A, IgM) and Complement ComponentC3	Waranu n Buajeeb	(41)
Patchtest	Patch test of dental materials in Oral Lichen Planus with consideringtheroleof saliva	2021	Amalgam(Mercury-based)	Farzane h Agha-Hosseini	(42)
Bloodtest	Diagnosis and managementoforal lichen planus	2021	Thyroid Function GlucoseLevel/HbA 1c HumanImmunodeficie ncy Virus (HIV) Liver Function CompleteBloodCou nt (CBC)	N Gururaj	(43)

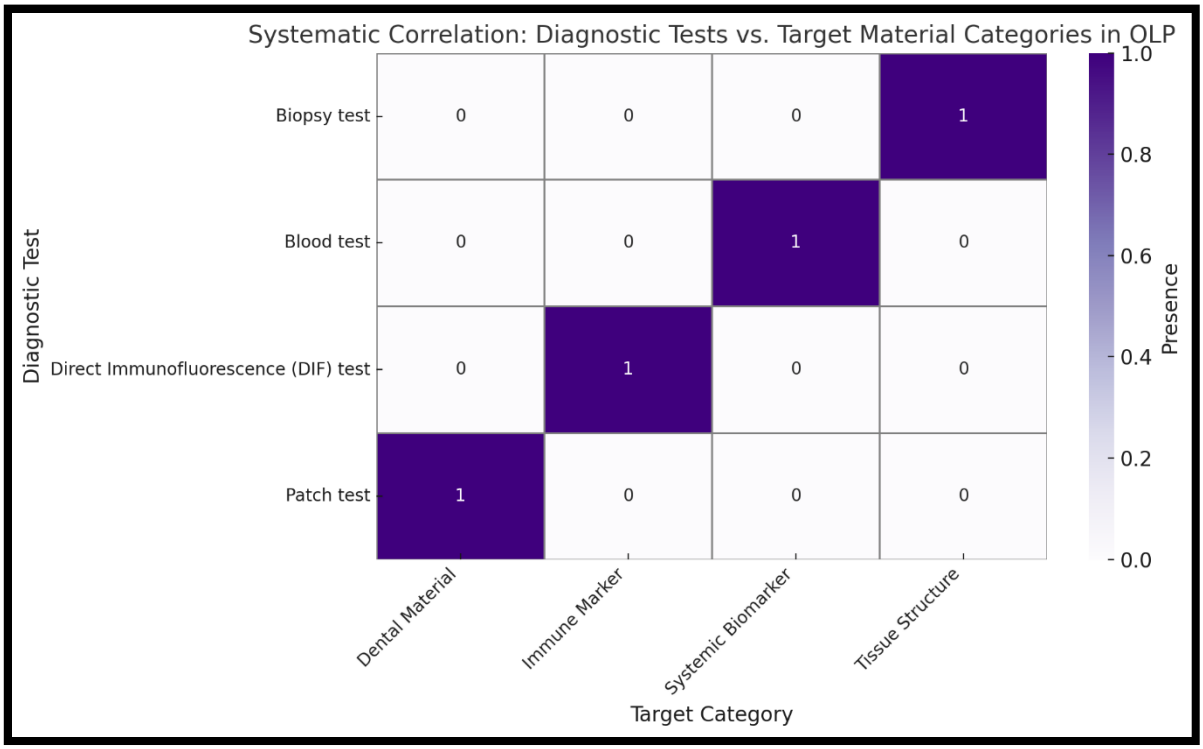

Figure 0-3: Systematic Correlation: Diagnostic Tests Vs. Target Material Categories In OLP.

3.4. Treatment in Oral Lichen Planus

The management of Oral Lichen Planus (OLP) focuses on reducing symptoms, controlling inflammation, and preventing disease progression. As there is no definitive cure, Management is adjusted according to the extent of symptoms and specific patient presentation. Conventional therapies include topical and systemic corticosteroids, while alternative and supportive treatments are gaining attention for their potential benefits and fewer side effects. The following table provides an overview of current treatment modalities used in OLP, highlighting their indications and mechanisms of action.

Table 0-4: Treatment in Oral Lichen Planus (44-57).

Methodoftreatment	**Titleofstudy**	**Year of population**	**Site**	**Nameof authors**	**Reference**
Surgicalexcision	OralLichenPlanus –A Brief Review on Treatment Modalities	2017	Buccalmucosa(inner cheeks) TongueGingiva(gums) Lips Palate(roofofthe mouth)	Nswan	(44)
Systemic Corticosteroids	DifferentTreatment Modalities of Oral Lichen Planus—A Narrative Review	2023	Oral mucosa ‘Skin‘ Genital lichen planus ‘ Scalp – Lichen planopilaris‘Esophageal lichen‘Nail lichen planus	AnaAndabak- Rogulj	(45)
Antibiotics(Antibiotics)	DifferentTreatment Modalities of Oral Lichen Planus—A NarrativeReview	2023	gingivallesions	AnaAndabak- Rogulj	(45)
Antimalarial Drugs (Hydroxychloroquine sulfate)	DifferentTreatment Modalities of Oral Lichen Planus—A NarrativeReview	2023	Oral cavityandlip	AnaAndabak- Rogulj	(45)
Glycyrrhizin	DifferentTreatment Modalities of Oral Lichen Planus—A NarrativeReview	2023	Oralcavity	AnaAndabak- Rogulj	(45)

AloeVera	DifferentTreatment Modalities of Oral Lichen Planus—A NarrativeReview	2023	Oralmucosa,skinand Genitals	AnaAndabak- Rogulj	(45)
Cyclosporine(CSA)	DifferentTreatment Modalities of Oral Lichen Planus—A NarrativeReview	2023	Skinand oral mucosa	AnaAndabak- Rogulj	(45)
Tacrolimusand Pimecrolimus	DifferentTreatment Modalities of Oral Lichen Planus—A NarrativeReview	2023	Skinand oralmucosa	AnaAndabak- Rogulj	(45)
Azathioprine	AzathioprinefortheTreatmentofSevere Erosive Oral and Generalized Lichen Planus	2001	Oralmucosa and skin	Kaushal K. Verma	(46)
Levamisole	Oral lichen planus: comparativeefficacyand treatment costs-a systematicreview	2022	Oralmucosa	SandhuS	(47)
Phenytoin	Oral lichen planus: comparativeefficacyand treatment costs-a systematicreview	2022	Oral mucosa, skin, Genital,Nail,andScalp	SandhuS	(47)
PhotodynamicTherapy (PDT)	PhotodynamicTherapy inTreatmentofOral Lichen Planus	2015	Oralmucosa and skin	DianaMostafa	(48)
Low-LevelLaser Therapy(LLLT)	LichenPlanopilarisand Low-Level Light Therapy: Four Case Reports and Review of theLiteratureAbout Low-Level Light	2020	LLLT is most commonlyusedinthe oral and cutaneous formsoflichenplanus but can also have	MichaelJ Randolph	(49)
NAVSNaphthalan	Topical NAVS naphthalan for the treatmentoforallichen planus and recurrent aphthous stomatitis: A double blind, randomized,parallel group study	2021	Oralmucosa and skin	AnaAndabak Rogulj	(50)
Selenium	Thiacalixarene assembled heterotrinuclear lanthanide clusters comprising Tb(III) and Yb(III) enable f-f communication to enhanceYb(III)-centred luminescence	2016	Oralmucosa and skin	Ryunosuke Karashimada	(51)

VitaminD	Evaluationofserum vitamin D levels in patients with lichen planus	2020	Oralmucosa and skin	DenizAksu Arıca	(52)
Curcumin	Comparisonoforal Nano-Curcuminwithoral prednisolone on oral lichen planus: a randomized double-blindedclinicaltrial	2020	Oralmucosa and skin	seyedlavadkia	(53)
Reflexo-Therapy	Themethodsofmodern reflexotherapy in the combined treatment of patients with erosive-ulceративeprocessesof the oral mucosa.	1991	buccal mucosa	LN Maksimovskaia	(54)
Hyaluronic Acid	Theefficacyoftopical hyaluronic acid in the management of oral lichenplanus	2009	Oralmucosa,skinand Genitals	Anoian	(55)
Retinoids	"Topicalretinoidsinoral lichenplanustreatment: an overview"	2013	Oralmucosa	Massimo Petruzzi	(56)
Tetracyclines	Topical Tetracycline TreatmentofErosive Oral Lichen Planus	1999	gingivallesions	Monika walcknr	(57)

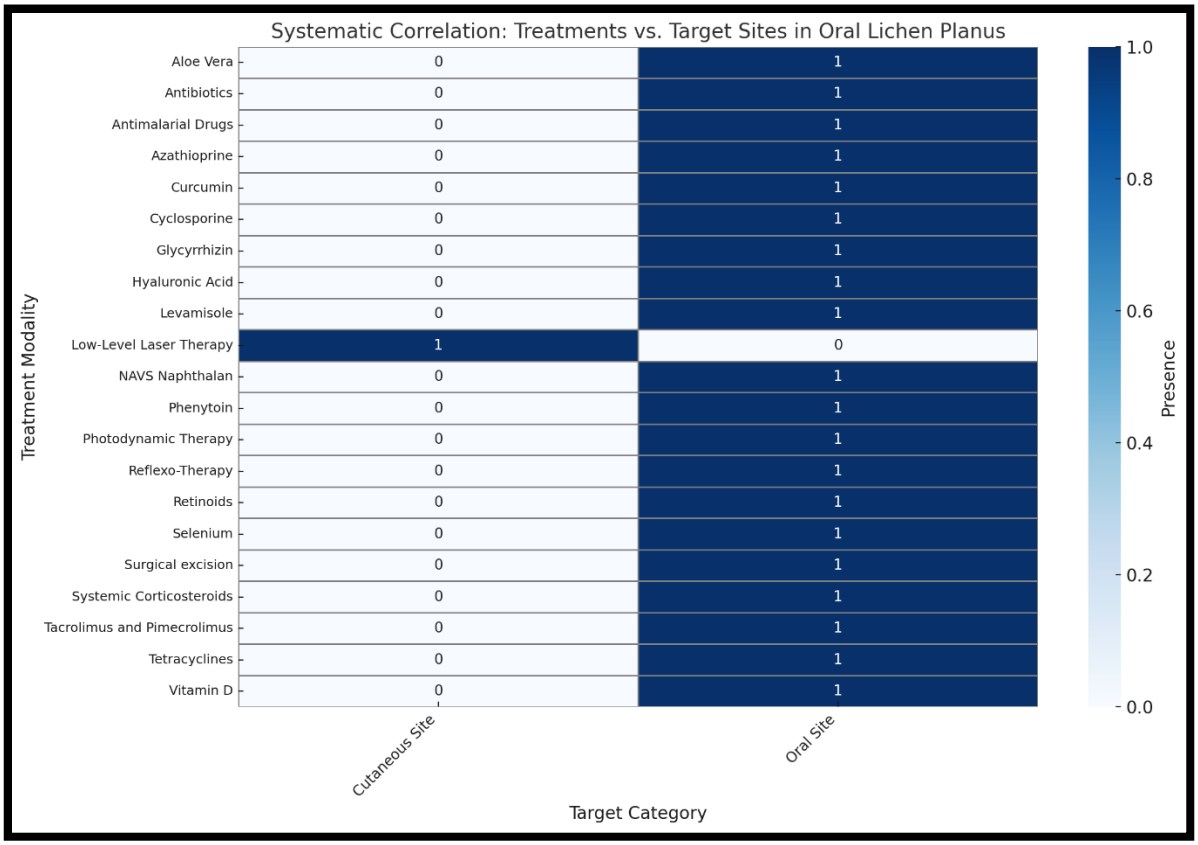

Figure 0-4: Systematic Correlation: Treatments Vs. Target Sites In Oral Lichen Planus.

3.5. Degree of Effect in Oral Lichen Planus

The clinical severity of Oral Lichen Planus (OLP) can vary significantly depending on the anatomical site involved. Specific oral mucosal sites exhibit increased susceptibility to chronic lesions, recurrent symptomatic exacerbations, and functional compromise, significantly affecting patient-reported outcomes. Assessing the degree of effect at different sites helps guide treatment decisions and monitor disease progression. The table below summarizes the typical severity associated with various oral locations affected by OLP.

Table 0-5: Degree of Effect in Oral Lichen Planus (58-63)

Siteofolp	Titleofstudy	Year of population	Degree ofeffect	Nameof authors	Reference
BuccalMucosa (Cheeks)	Theclinicalfeatures,malignant potential, and systemic associations of oral lichen planus:Astudyof723patients.	2002	Severity:Canrange from mild asymptomatic lesions to painful erosiveulcers.	Eisen,D	(58)
Tongue	Oral lichen planus and its malignantpotential:Aclinical review	2014	(modratetosever) Erosive and ulcerativeformsare painful, affecting speechandeating.	Maderal,A. D.	(59)
Gingiva	Themanagementandprognosis of oral lichen planus. Oral lichenplanus:Adiseaseora spectrumoftissuereactions? Types, causes, diagnostic algorhythms, prognosis, management strategies	2019	(modrate) Can causegumpainand sensitivity,making oralhygiene difficult.	MCarrozz	(60)
Palatal	Worldwideprevalenceoforal lichenplanus:Asystematic review and meta-analysis.	2021	Mild(reticular)or modrate (erosive)	Gonzalez-Moles,M.	(61)
Floorofthe Mouth	Currentcontroversiesinoral lichen planus: report of an international consensus meeting. Part 1. Viral infections and etiopathogenesis.	2005	Mild(reticular)or modrate (erosive)	Lodi G	(62)
Lips	Malignanttransformationof atypicalorallichenplanus:a review of 32 cases.	2003	Severity:Can range accordingtoclinical presentation from mild (reticular) or modrate (plaque - like or atrophic) or sever(erosiveor bullous	Lanfranchi-Tizeira	(63)

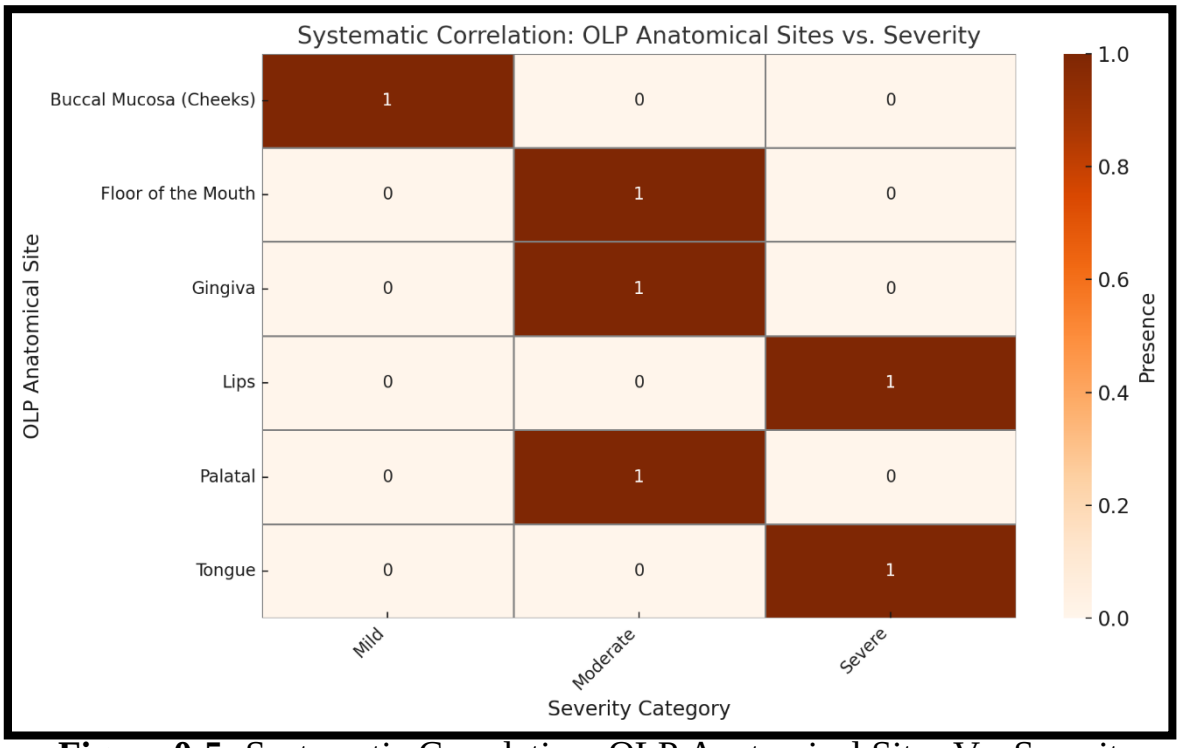

Figure 0-5: Systematic Correlation: OLP Anatomical Sites Vs. Severity.

3.6. Psychological Effects of Oral Lichen Planus (OLP) and Treatment effects

Beyond physical symptoms, Oral Lichen Planus (OLP) and its treatment can have notable psychological implications. Chronic pain, aesthetic concerns, and long-term use of medication may lead to anxiety, stress, or reduced quality of life in some patients. Understanding the emotional and psychological burden of both the disease and its management is essential for providing comprehensive care.

The table below highlights common psychological responses observed during OLP treatment and their potential impact on patient well-being.

Table 0-6: Psychological Effects of Oral Lichen Planus (OLP) and Treatment effects (64-66)

Aspect	Effect	Examples | note	Title of study	Source	Reference
Disease Impact	Anxiety, depression,	Due to pain, visible	Oral disease	Zamarrón et al.,	(64)

	low self-esteem	lesions, and chronicity		2020;	
Corticosteroid	Mood swings, depression, anxiety	Affects brain chemistry during long-term use	Journal of Psychosomatic Research	Klinge et al., 2014	(65)
Immunosuppress	Fatigue, irritability, emotional instability	Cyclosporine and azathioprine	International Journal of Pharmacy and Pharmaceutical Sciences,	Soni et al., 2018	(66)

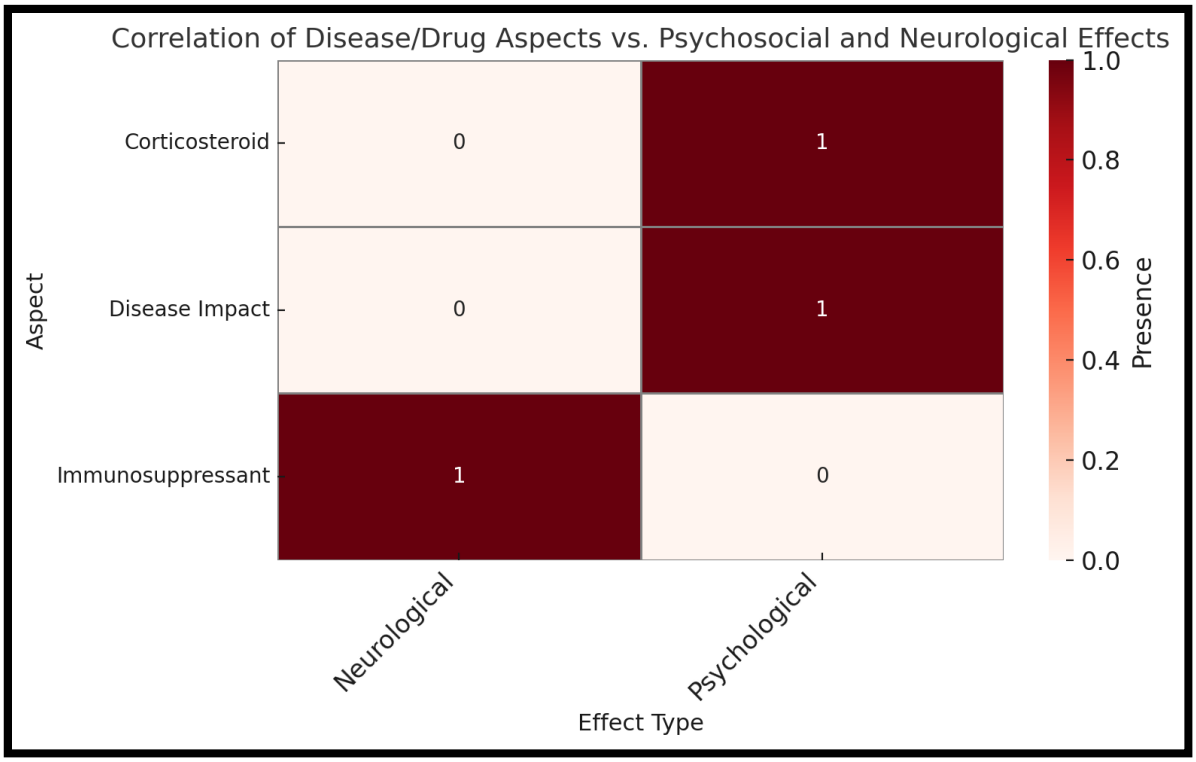

Figure 0-6: Correlation Of Disease/Drug Aspects Vs. Psychosocial And Neurological Effects.

Chapter four

Discussion

4. Chapter four: Discussion

4.1. Immune Mechanisms in Oral Lichen Planus

4.1.1. Interlukin-1

The persistent presence of IL-1 helps explain why OLP often follows a chronic, relapsing course. Its ability to maintain local immune activation creates an environment where normal healing processes are suppressed while tissue-destructive pathways remain active. This molecular understanding may guide future targeted therapies aimed at interrupting the IL-1 signaling axis, Studies demonstrate that this potent cytokine acts as a molecular alarm signal within oral tissues, triggering a cascade of immune events that perpetuate disease pathology The mechanisms through which IL-1 drives OLP progression are multifaceted:

- Immune Cell Recruitment: IL-1 serves as a powerful chemoattractant, drawing various immune cells into the oral epithelium and creating the characteristic dense inflammatory infiltrate seen histologically.

- Cytokine Network Activation: Once present, these activated immune cells release additional inflammatory mediators, establishing a self-sustaining cytokine loop. Epithelial-Stromal Cross-talk: IL-1 facilitates damaging interactions between epithelial cells and underlying connective tissue, disrupting normal mucosal architecture (67) .

4.1.2. Interleukin-2

Multifaceted Role in OLP Pathogenesis ,The resistance of some cases to topical The cytokine IL-2 emerges as a master regulator in OLP's complex immune landscape, regulating multiple pathological events by exerting varied effects across immune cell types. Its involvement extends far beyond simple T-

cell stimulation, shaping the very nature of the autoimmune response characteristic of this condition.

4.1.1.1. Mechanistic Insights:

- T-Cell Dynamics: IL-2 acts as both an initiator and amplifier of T-cell responses, particularly driving the expansion of autoreactive CD8+ T-cells that directly attack keratinocytes.

- Immunological Memory: By stimulating the survival of memory T-cells, IL-2 helps maintain long-term immune reactivity against oral mucosal antigens.

- Cytokine Cross-Talk: IL-2-induced signaling enhances the production of other inflammatory mediators like IFN-γ, creating a synergistic pro-inflammatory milieu.

Clinical Implications

The persistent IL-2 activity in OLP lesions explains several clinical observations:

- The infiltrate-rich histopathology dominated by T-cells

- The chronic, relapsing nature of the disease therapies (68).

4.1.3. Interleukin-4

Is an important immunomodulatory cytokine that typically encourages the development of Th2 cells while downregulating Th1-driven immune responses. This function plays a key role in maintaining immune equilibrium and preventing overly aggressive inflammation. In individuals affected by Oral Lichen Planus (OLP), however, this regulatory function seems impaired. a disrupted ratio of IFN-γ to IL-4 reflects a skewing toward Th1-type responses. This immunological shift likely sustains the chronic inflammatory state characteristic of OLP, as Th1-derived cytokines

predominate and perpetuate immune-mediated mucosal injury (69).

4.1.4. Interleukin-5

IL-5 is primarily involved in the development, activation, and recruitment of eosinophils, which are white blood cells often associated with allergic reactions and certain inflammatory conditions.Eosinophils likely contribute as secondary players in exacerbating localized immune responses. Although the exact involvement of IL-5 and eosinophils in OLP pathogenesis requires further elucidation, their detection within lesions suggests a sophisticated immunological network—possibly encompassing interrelated pathways that perpetuate inflammatory cycles and mediate tissue damage (70).

4.1.5. Interleukin-6

Is widely known as an inflammatory marker, but its role extends beyond that—it significantly influences the activity and survival of CD8+ T cells, which are key players in the destruction of keratinocytes in Oral Lichen Planus (OLP). By enhancing the activation and persistence of these cytotoxic T cells in the affected tissue, IL-6 inadvertently fuels the ongoing tissue damage. As these T cells continue to attack, they target the basal layer of the oral mucosa, promoting keratinocyte death and accelerating the development of lesions (71).

4.1.6. TGF-β

Plays a dual role in inflammation, acting as both a suppressor and promoter depending on the context. In Oral Lichen Planus (OLP), it drives fibroblasts to become myofibroblasts, leading to excessive extracellular matrix production. This fibrotic reaction results in rigid, scarred mouth tissues. Bacterial infections like P. gingivalis can trigger this pathway by activating TGF-β signaling. Chronic activation contributes to persistent lesions and discomfort in OLP patients (72).

4.1.7. IFN-γ

Plays a central role in the immune-mediated pathology of OLP by activating the JAK2/STAT1 signaling pathway, which amplifies the immune system’s

cytotoxic activity. It simultaneously increases the expression of MHC class I molecules on keratinocytes, improving their visibility to CD8+ T cells. This heightened immune recognition leads to keratinocyte apoptosis and targeted destruction. The cumulative effect of these actions results in persistent inflammation and epithelial damage, which are key features of oral lichen planus (73).

4.1.8. TNF-α

Is a key inflammatory cytokine elevated in Oral Lichen Planus (OLP), playing a critical role in disease progression. It activates the NF-κB signaling pathway via TNFR1/TNFR2 receptors, Aggravating inflammation. TNF-α induces keratinocyte apoptosis directly and through Fas/FasL interactions, contributing to tissue damage. Chronic inflammation leads to fibrosis, scarring, and impaired wound healing. Elevated salivary TNF-α levels could serve as a biomarker for monitoring OLP(74).

4.2. Microbial Pathogens in Oral Lichen Planus

4.2.1. Helicobacter pylori

widely recognized for its role in gastric pathologies , has also been implicated in oral disorders, including Oral Lichen Planus (OLP). The pathogen generates reactive oxygen species (ROS), triggering oxidative damage within oral mucosal cells. This cellular injury promotes programmed cell death (apoptosis) .compromising the integrity of the oral epithelial barrier.

The disruption of this protective layerheightens vulnerability to immune-mediated destruction ,thereby worsening OLP manifestations

. Emerging evidence indicates that H. pylori infection may influence disease progression and clinical severity in OLP patients (75).

4.2.2. Fusobacteriumnucleatum

Prominent oral pathogen traditionally associated with periodontal diseases, has now been implicated in the pathogenesis of Oral Lichen Planus (OLP).

Emerging evidence demonstrates that F. nucleatum exhibits tissue-invasive capabilities, penetrating beyond superficial layers to colonize deeper connective tissues. During this process, the bacterium secretes proteolytic enzymes that degrade extracellular matrix components, compromising tissue architecture and mechanical stability.

Furthermore, F. nucleatum functions as a potent immunomodulator, stimulating excessive production of inflammatory mediators including tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β). In the context of OLP - a condition characterized by pre-existing mucosal vulnerability - this bacterial activity exacerbates the chronic inflammatory milieu. The resulting positive feedback loop perpetuates epithelial destruction and contributes to local immune dysregulation, potentially worsening disease progression and clinical manifestations (76).

4.2.3. Hepatitis C Virus (HCV)

Has been associated with Oral Lichen Planus (OLP) through its immunomodulatory effects. The virus modifies the biochemical composition of the oral mucosa, resulting in immune dysregulation. HCV induces either cytotoxic T lymphocyte activation or stimulates B-cell responses that generate autoantibodies, leading to erroneous targeting of host tissues. This aberrant immune activity perpetuates sustained inflammatory processes and epithelial injury characteristic of OLP. The synergistic relationship between HCV and OLP aggravates disease manifestations, resulting in chronic, recalcitrant oral lesions (77).

4.2.4. Human Herpesvirus 7

Emerging evidence implicates Human Herpesvirus 7 (HHV-7) in the pathogenesis of Oral Lichen Planus (OLP) through its tropism for plasmacytoid dendritic cells (PDCs) within oral mucosal tissues. Following viral entry, HHV-7 triggers PDC activation, resulting in excessive secretion of proinflammatory

cytokines (particularly TNF-α, IL-6) and type I interferons (IFN-α/β). This persistent cytokine storm sustains a chronic inflammatory microenvironment characteristic of OLP lesions (78).

The continuous HHV-7-mediated PDC stimulation disrupts local immune homeostasis, promoting cytotoxic T-cell responses that drive epithelial apoptosis and basement membrane disruption. Notably, clinical observations demonstrate an inverse relationship between HHV-7 viral load and disease activity, with OLP remission periods corresponding to diminished viral protein expression.

These findings suggest that targeted antiviral strategies against HHV-7 may represent a promising therapeutic approach for OLP management, potentially interrupting the cycle of chronic inflammation and facilitating mucosal healing.

4.2.5. Candida albicans

Has been implicated in the potentially malignant progression of Oral Lichen Planus (OLP) through multiple oncogenic pathways. The fungus generates carcinogenic nitrosamine compounds that can induce proto-oncogene activation and subsequent dysregulated cellular proliferation. Persistent C. albicans colonization establishes a chronic inflammatory state characterized by:

- Sustained epithelial microtrauma

- Reactive oxygen species (ROS)-mediated oxidative injury

- Genomic instability in oral keratinocytes

This pro-carcinogenic microenvironment leads to:

1. Cell cycle checkpoint dysfunction

2. Impaired apoptosis signaling

3. Epithelial-mesenchymal transition markers

Particularly in erosive and atrophic OLP variants, the cumulative effects of chronic candidal infection may significantly elevate malignant transformation risk by promoting progressive epithelial dysplasia. The fungal presence appears to synergize with OLP's inherent inflammatory pathology to accelerate tumorigenic processes (79).

4.2.6. Porphyromonasgingivalis

Significantly contributes to the chronicity and advancement of Oral Lichen Planus (OLP) via multiple pathogenic pathways. By destabilizing the equilibrium of the oral microbiome, it facilitates the overgrowth of harmful bacterial species, altering the ecological dynamics of the mucosal environment. Additionally, *P. gingivalis* assembles durable biofilms that act as a protective barrier, safeguarding embedded microbial populations from host immunological defenses and diminishing therapeutic outcomes.

Furthermore, this bacterium secretes potent virulence determinants, such as gingipain proteases, which dismantle essential host proteins and recalibrate immune signaling pathways. Collectively, these mechanisms perpetuate a state of prolonged inflammation, hinder tissue regeneration, and potentially exacerbate the severity of OLP manifestations progressively (80).

4.2.7. Prevotella intermedia

1. Inflammatory Activation – P. intermedia releases harmful compounds (such as endotoxins and enzymes) that trigger immune sensors (TLRs) and inflammatory signaling (NF-κB), increasing destructive cytokines (IL-1β, IL-6, TNF-α, IL-17). This strengthens Th1/Th17 immune reactions involved in OLP progression (81).

2. Microbial Imbalance – During gum disease or oral inflammation, P. intermedia flourishes with other harmful bacteria (like Porphyromonasgingivalis), while suppressing beneficial bacteria (such as

Streptococcus salivarius) that protect the oral lining. This disruption may sustain long-term tissue irritation (82).

3. Immune System Disruption – P. intermedia encourages excessive Th17 activity and weakens regulatory T-cell (Treg) function, worsening OLP's inflammation. Its ability to form sticky bacterial clusters also makes it harder to eliminate (83).

4. Slowed Tissue Repair – By maintaining a highly inflamed environment and damaging tissue structure (through enzyme activity), it can delay healing, making erosive or ulcerative OLP lesions more severe (84).

4.2.8. Tannerella forsythia

Periodontal pathogen Tannerella forsythia has been implicated in the development and progression of oral lichen planus through multiple mechanisms. By disturbing the natural equilibrium of oral microbiota, this bacterium creates a dysbiotic environment favorable for disease progression. T. forsythia secretes pathogenic components including the BspA surface protein and various glycosidases, which compromise host tissues and stimulate pattern recognition receptors like TLRs. This interaction initiates a cascade of inflammatory mediators, particularly interleukin-1 beta and tumor necrosis factor-alpha, resulting in compromised epithelial integrity and abnormal immune responses.

The microorganism's capacity to establish complex microbial communities enhances its survival within the oral cavity while evading host defense mechanisms. This persistent colonization maintains a state of chronic immune activation and tissue damage, which are hallmarks of OLP pathology. The continuous cycle of microbial persistence, inflammatory mediator release, and epithelial injury appears to play a significant role in sustaining the chronic nature of this mucosal disorder (85).

4.2.9. Streptococcuss anguinis

A beneficial pioneer colonizer of the oral cavity, plays a critical role in maintaining microbial homeostasis by inhibiting pathogenic overgrowth, particularly of species like Porphyromonasgingivalis. This commensal bacterium promotes oral health through multiple mechanisms, including hydrogen peroxide production and competitive exclusion at adhesion sites, effectively suppressing harmful microorganisms.

Emerging research has identified a significant reduction in S. sanguinis populations within Oral Lichen Planus (OLP) lesions. This depletion disrupts the delicate microbial equilibrium, creating a dysbiotic state that favors pathogen dominance. The consequent microbial imbalance may intensify immune dysfunction and perpetuate chronic inflammatory responses, potentially worsening OLP progression and clinical manifestations (86).

4.2.10. E. coli

May play a hidden yet impactful role in the progression of Oral Lichen Planus (OLP) by integrating into the deeper layers of oral tissues. Once inside, it releases endotoxins like LPS, which interact with TLR4 receptors on immune cells, setting off a wave of pro-inflammatory cytokines such as TNF-α and IL-6. This immune activation heightens T-cell aggression, leading to increased destruction of epithelial cells. In parallel, the inflammation disrupts the integrity of the mucosal lining, lowering its defense. The result is a self-sustaining loop of tissue damage and chronic inflammation commonly seen in OLP (87).

4.2.11. Candida glabrata

Has been implicated in the pathogenesis of oral lichen planus (OLP) through multiple mechanisms that promote chronicity and treatment resistance. This opportunistic fungal pathogen demonstrates an exceptional ability to evade immune detection while establishing persistent mucosal colonization. Its intrinsic resistance to azole antifungals and capacity for biofilm formation create therapeutic challenges, allowing the organism to withstand both

pharmacological treatments and host defenses. The sustained presence of *C. glabrata* perpetuates a state of low-grade inflammation through continuous antigenic stimulation and epithelial disruption. These factors collectively contribute to delayed healing and symptom persistence in OLP. The recognition of *C. glabrata*'s role suggests the need for alternative management strategies, including advanced antifungal regimens and biofilm-targeting approaches, to improve clinical outcomes in affected patients (88).

4.2.12. Candida tropicalis

Contributes to the progression of oral lichen planus (OLP) through several distinct mechanisms. This fungal pathogen promotes a heightened inflammatory response by triggering excessive production of inflammatory signaling molecules, including tumor necrosis factor-alpha and interleukin-6, which intensify the inflammatory milieu characteristic of OLP lesions. The organism's ability to establish long-term colonization in oral tissues helps perpetuate this inflammatory condition, leading to ongoing mucosal injury.

Furthermore.tropicalis appears to interfere with normal immune cell communication pathways, resulting in dysfunctional immune regulation and delayed tissue repair. In patients with compromised immune function or those receiving extended therapeutic interventions, the fungus may evade normal immune surveillance more effectively, thereby amplifying clinical manifestations and extending the duration of inflammatory episodes. These observations highlight the potential role of *C. tropicalis* in maintaining the chronic nature of OLP and suggest that its presence may influence disease severity and treatment outcomes (89).

4.3. Diagnostic Evaluation in Oral Lichen Planus

4.3.1. biopsy test

Plays a vital role in definitively diagnosing Oral Lichen Planus (OLP), especially in cases where clinical signs are ambiguous. Microscopic analysis of

the tissue usually reveals hallmark features such as epithelial thickening (hyperkeratosis), elongation of the spinous layer (acanthosis), and distinctly pointed rete pegs. One of the most defining characteristics is basal cell degeneration, which can result in the formation of Max Joseph clefts—small separations between the epithelium and the connective layer beneath. Additionally, a prominent band of lymphocytes is typically present just below the epithelial layer, and apoptotic keratinocytes known as Civatte bodies can be observed at the junction between the epithelium and connective tissue. There may also be an accumulation of fibrin appearing as an eosinophilic layer beneath the basement membrane. In certain situations, direct immunofluorescence testing is used to identify fibrinogen deposits along the BMZ, which assists in ruling out similar conditions. biopsy is a critical tool for differentiating OLP from other oral lesions and for assessing any potential for malignant transformation (90).

4.3.2. Direct Immunofluorescence (DIF) testing

Is an important diagnostic tool for confirming Oral Lichen Planus (OLP), especially when other tests are inconclusive. This test uses special dyes to detect immune proteins in tissue samples. the most common feature in OLP is the linear deposition of fibrinogen along the basement membrane zone (BMZ), which appears brightly fluorescent under the microscope. Additionally, immunoglobulins (IgG, IgA, IgM) and complement component C3 can sometimes be detected, although they are less consistent. These immune markers help confirm that OLP is an immune-mediated condition and can help differentiate it from other similar conditions, such as pemphigoid or lupus erythematosus (91).

4.3.3. Patch test

It a widely used diagnostic tool for identifying contact allergens, particularly in conditions like Oral Lichen Planus (OLP). A recent study examined materials such as amalgam, which contains mercury, and its potential role in exacerbating allergic reactions. It was found that mercury in amalgam could potentially trigger or aggravate OLP lesions in sensitive individuals. The patch test serves to identify whether dental materials are contributing to the ongoing inflammation in OLP, offering a valuable diagnostic approach that aids in customizing patient treatment plans and management(92).

4.3.4. Blood tests

Are crucial in diagnosing and managing Oral Lichen Planus (OLP), as demonstrated in a 2021 study by N. Gururaj. The tests facilitate evaluation of several physiological factors capable of altering the disease state. Important tests include thyroid function, since abnormalities can affect the immune system; glucose levels and HbA1c, to monitor diabetes, which is linked to immune imbalance in OLP; HIV tests, as the virus can compromise the immune system, making individuals more prone to OLP; liver function tests, as liver diseases can worsen the symptoms; and a complete blood count (CBC) to check for anemia, infection, or inflammation, which could complicate OLP. These tests are not only essential for diagnosing OLP but also for managing any related health conditions that might affect treatment and disease progression (93).

4.4. Treatment in Oral Lichen Planus

4.4.1. Surgical removal

Is sometimes considered for treating oral lichen planus, particularly in advanced cases where the oral tissues are significantly damaged. The procedure involves taking out the affected areas, which can help ease discomfort and improve the patient’s overall condition.

According to a 2017 study that reviewed various treatment options for OLP, surgical intervention is typically used when medication doesn't lead to improvement or when the disease becomes more aggressive, spreading to several parts of the mouth—such as the inner cheeks, tongue, gums, lips, and the palate.

This approach can play a key role in reducing long-term symptoms like persistent pain or inflammation, and in certain cases, it may lower the risk of complications like malignant transformation (94).

4.4.2. Systemic corticosteroids

Are an effective treatment for severe or widespread cases of oral lichen planus, especially when multiple areas of the body are affected. This treatment works by reducing inflammation and suppressing the excessive immune response. It is particularly helpful for cases involving the oral mucosa, skin, genital areas, scalp (such as Lichen planopilaris), esophagus, and nails. Systemic corticosteroids are typically used when topical treatments are insufficient or when the condition is more severe (95).

4.4.3. Antibiotics

Can be considered in the treatment of oral lichen planus, particularly when the condition affects the gums. Although they're not a first-line therapy, they may be useful in controlling bacterial infections that can develop due to open sores or ongoing inflammation. In such cases, antibiotics help reduce bacterial activity, limit further irritation, and support the healing process—especially when there's a chance of bacterial complications occurring alongside the underlying condition (96).

4.4.4. Hydroxychloroquine

originally used for malaria, has shown effectiveness in treating certain cases of oral lichen planus, especially when it involves the lips and inner lining of the mouth. It works by calming down the immune system's overactivity, which is a

key factor in this condition. This medication is usually considered when the disease doesn't respond well to other treatments. It's particularly helpful for patients with more persistent or widespread symptoms, offering an alternative when standard therapies fall short (97).

4.4.5. Glycyrrhizin

a natural compound extracted from licorice root, has been explored as a treatment for oral lichen planus due to its anti-inflammatory and immune-regulating properties. It helps reduce irritation and promotes healing in the oral mucosa. This remedy is especially considered in milder cases or when patients prefer a more natural or herbal approach. It may not replace conventional medication entirely, but it can be a supportive option for symptom relief and inflammation control (98).

4.4.6. Aloe Vera

Has been used as a soothing agent in the treatment of oral lichen planus, especially when the condition affects the mucous membranes, skin, or even the genital area. Thanks to its calming and anti-inflammatory effects, it can help ease discomfort and support tissue healing. While it's not a primary treatment, aloe Vera may be a useful addition—particularly for those looking for gentler, plant-based alternatives to conventional medications. It's often used in gel or rinse form to target irritated areas directly (99).

4.4.7. Cyclosporine

Is an immunosuppressive medication that's sometimes used to treat oral lichen planus, especially when the condition involves both the skin and the lining of the mouth. Its main role is to reduce the activity of the immune system, which helps limit the inflammation responsible for the symptoms. This treatment is generally considered in more stubborn or widespread cases, particularly when other options like corticosteroids haven't been effective. It's often applied topically as a mouth rinse or used systemically under medical supervision (100).

4.4.8. Tacrolimus and pimecrolimus

Are non-steroidal topical treatments that help manage oral lichen planus by targeting immune-related inflammation. They are particularly useful in cases where the condition affects both the skin and the mucosal tissues of the mouth. These medications work by modulating the immune response, helping to reduce symptoms like redness, irritation, and discomfort. Often recommended when corticosteroids are either ineffective or not well tolerated, they offer an alternative for long-term management without some of the side effects linked to steroid use (101).

4.4.9. Azathioprine (AZA)

Is a medication that interferes with purine synthesis, which helps reduce the growth of T and B lymphocytes (a type of white blood cell). In addition to its immune-suppressing effects, it also has important anti-inflammatory properties. AZA is used for more widespread cases of oral lichen planus, but it must be used carefully due to serious potential side effects, such as bone marrow suppression, reduced blood cell production (pancytopenia), and liver problems. It is usually given systemically under close medical supervision (102).

4.4.10. Levamisole

Has been used as an immune system modulator in treating oral lichen planus (OLP). A study suggests that combining low doses of systemic corticosteroids with levamisole can help control the more severe erosive form of OLP. However, it has been observed that some patients using levamisole for rheumatoid arthritis developed lichenoid lesions both on their skin and in the mouth. These lesions disappeared once levamisole treatment was stopped (103).

4.4.11. Phenytoin

was used to treat oral lichen planus (OLP), with complete healing observed in two out of four patients. However, further research did not confirm its effectiveness in treating OLP, nor did it show any significant side effects from

the treatment. It is also known that phenytoin can sometimes cause lichenoid lesions to appear (104).

4.4.12. Photodynamic therapy (PDT)

It works by combining light with a photosensitizer (PS), PDT was as effective as topical corticosteroids and can be used for OLP that does not respond to corticosteroids or when they cannot be used. However, there are some limitations, such as the small number of studies, differences in how the studies were conducted, and variations in treatment settings. More high-quality studies are needed to confirm these findings (105).

4.4.13. Low-level laser therapy (LLLT)

Is a treatment option for oral lichen planus (OLP), with some studies showing positive results, such as complete healing after two sessions. However, there is no universally accepted protocol for this treatment. A review of studies found that corticosteroids were more effective than LLLT in most cases. Another study showed that PBM (photobiomodulation) with laser therapy was effective in reducing symptoms, but the results were limited due to small sample sizes and lack of follow-up (106).

4.4.14. NAVS (Naphthalan)

Is an earth mineral oil with chemical structures similar to vitamin D3 and steroid hormones. Two studies evaluated its effectiveness in treating oral lichen planus (OLP). A pilot study showed clinical improvements in 11 OLP patients. In a controlled trial with 39 patients, both NAVS and betamethasone oral paste led to improvements, but there were no significant differences in disease activity or pain intensity between the two groups. NAVS had no side effects, while betamethasone caused a candida infection in three patients. Due to the small sample size, more studies are needed to confirm these findings (107).

4.4.15. Selenium (Se)

An antioxidant with various health benefits, was tested in a clinical trial for treating erosive oral lichen planus (OLP). Two forms of selenium (topical

hydrogel and oral capsules) were compared with topical corticosteroids. After 6 weeks of treatment, all groups showed improvements, but no significant differences were found between them. Selenium had advantages over corticosteroids, including longer-lasting effects, better pain relief, and no increased risk of infections. However, more studies with larger sample sizes are needed (108).

4.4.16. Vitamin D

Plays a key role in immunity. A study showed significant improvement in OLP symptoms with vitamin D supplementation, especially when combined with psychological support and topical steroids. Despite a small sample size, vitamin D's potential in treating OLP was noted. A larger study also found that patients with vitamin D supplementation had the best results (109).

4.4.17. Curcuma longa (Curcumin)

Has anti-inflammatory and antioxidant properties, and a study in 2015 compared its effectiveness to triamcinolone in treating oral lichen planus (OLP). Both treatments showed similar results in reducing pain, with no major side effects from curcumin, though some patients reported mild discomfort. The study suggested curcumin could be a natural alternative to synthetic drugs for OLP, and other research has proposed it as a maintenance treatment after corticosteroids. However, not all studies found curcumin effective for OLP (110).

4.4.18. Reflexology

Has been explored as a treatment option for symptomatic oral lichen planus (OLP) in some studies. Various treatment approaches are suggested to promote the healing (epithelization) of erosive lesions and ulcers, particularly on the buccal mucosa (inner cheek area). Reflexology is also noted for its significant pain-relieving (analgesic) effects, helping to ease discomfort in patients with OLP (111).

4.4.19. Topical hyaluronic acid (HA) gel

Has been tested as a treatment for erosive oral lichen planus (OLP). A randomized, double-blind study found that HA gel significantly reduced soreness for up to 4 hours after application. Over 28 days of treatment, the lesion size also decreased, though there was no significant difference in size between the treatment and placebo groups. This suggests HA gel may be a helpful addition to OLP treatment when used frequently. Additionally, a comparison of HA (0.2%) and triamcinolone (TA) (0.1%) showed improvements in pain and lesion size in both treatments, with no significant difference between them (112).

4.4.19. Retinoid

Which are derived from vitamin A, are used to treat oral lichen planus (OLP) either topically or systemically. They play an important role in the growth and regeneration of epithelial cells. Topical retinoids like tretinoin, isotretinoin, and fenretinide (0.1% gel) help reduce reticular and plaque lesions, but recurrence may happen once treatment is stopped. Systemic retinoids, such as etretinate, isotretinoin, and tretinoin, are less commonly used due to side effects like cheilitis, liver damage, and teratogenic effects. However, temarotene, a systemic retinoid, has been found effective in treating OLP with fewer side effects (113).

4.4.20. Tetracycline

Have been utilized in treating OLP, but their effectiveness is generally limited to specific cases involving gingival lesions. Currently, antibiotics are not advised as a standard treatment for OLP (114).

4.5. Degree of Effect in Oral Lichen Planus

4.5.1. The buccal mucosa

Is one of the most frequently affected sites in people with oral lichen planus (OLP). In many cases, the condition appears as thin, white, web-like lines, but it

can also develop into more painful erosive lesions that affect daily activities like eating and talking. Although the majority of cases remain non-cancerous, a small number can potentially turn into oral cancer—especially when the lesions are red or ulcerated. Triggers such as emotional stress, dental work, spicy foods, and poor oral hygiene may lead to flare-ups. Because of this, patients with OLP in the cheek area should be monitored regularly to catch any early signs of serious changes (115).

4.5.2. The tongue

Oral lichen planus (OLP) on the tongue is considered more severe and aggressive compared to other areas in the mouth. Lesions on the tongue are often painful, more resistant to treatment, and linked to a higher risk of malignant transformation, especially in the atrophic and erosive forms. Because of this, OLP on the tongue requires closer monitoring and more frequent follow-up, as it may progress to oral cancer in rare cases if left unchecked (116).

4.5.3. Gingiva

Oral lichen planus (OLP) can significantly impact the gingiva, especially in severe forms like erosive OLP. It can lead to gum pain and increased sensitivity, making daily oral care difficult. In advanced stages, it may cause damage to the gum tissue, leading to recession and a higher risk of infections and periodontal issues. Severe cases are characterized by painful ulcers, scarring, and changes in gum appearance. Treatment typically involves topical steroids or other therapies to manage symptoms and prevent further gum damage, though some patients may experience recurrent flare-ups. Effective management is essential for minimizing discomfort and tissue destruction (117).

4.5.4. Palate

Oral lichen planus (OLP) on the palate can vary in severity. Mild cases are characterized by localized lesions that cause minimal discomfort, with limited mucosal involvement and slight sensitivity. Moderate cases involve increased redness and some erosion of the palate, with more noticeable pain and

sensitivity, which can often be managed with topical treatments. In severe cases, extensive erosions or ulcers cause significant pain and difficulty eating, often requiring systemic treatment. These severe cases also have a higher risk of complications and potential malignant transformation, making early and aggressive intervention crucial (118).

4.5.5. The floor of the mouth

Scoring system has been developed to assess the severity of oral lichen planus (OLP), including lesions on the floor of the mouth. This system evaluates the extent of site involvement, disease activity, and pain severity. For floor-of-mouth lesions, it considers the percentage of the area affected, the level of inflammation or ulceration present, and the intensity of pain reported by the patient. The severity and activity scores are then combined to give a comprehensive assessment, helping standardize evaluations across clinical settings and studies (119).

4.5.6. The lip

The severity of oral lichen planus (OLP) affecting the lips is categorized into three levels. Mild cases are characterized by localized lesions with minimal symptoms. Moderate cases involve more extensive lesions with noticeable discomfort, while severe cases present with extensive lesions that cause significant pain and functional impairment. The article highlights that severe OLP on the lips is more likely to undergo malignant transformation, underscoring the importance of early detection and proper management to prevent complications (120).

4.6. Psychological Impact of Treating Oral Lichen Planus (OLP)

4.6.1. Anxiety and Depression

The persistent nature of oral lichen planus, along with its painful lesions and potential alterations in oral appearance, can have a notable effect on the

patient's mental health. In many cases, the psychological burden is intensified by the adverse effects of long-term medication use (121)(122).

• Effect on Patients: Chronic oral diseases like OLP have been linked to elevated levels of psychological distress, particularly anxiety and depression. The ongoing pain, burning sensation, and visible lesions may lead individuals to isolate socially, experience a decline in daily functioning, and suffer from lowered self-esteem. Several studies suggest that the unpredictable progression of the disease adds to the mental strain experienced by these patients (122)(123).

• Role of Psychological Support: Addressing the emotional well-being of OLP patients is essential. Incorporating mental health care—such as psychological counseling and peer support groups—into the overall treatment plan may improve patients' coping mechanisms and enhance quality of life (124).

4.5.7. Psychological Side Effects of Medications

4.1.1.2. Corticosteroids

Extended use of corticosteroids, often prescribed to manage inflammation in OLP, has been associated with mood-related side effects. These may include irritability, emotional instability, and depressive symptoms due to alterations in neurochemical pathways (125).

4.1.1.3. Immunosuppressants

Drugs such as cyclosporine and azathioprine, while effective in controlling immune activity, may lead to fatigue, emotional blunting, and heightened sensitivity to stress. These side effects are thought to stem from both the immune-suppressive properties and the general physiological burden placed on the patient (126)(127).

4.6. Conclusion

1. Oral lichen planus (OLP) is a long-standing condition of the mouth that mainly involves immune system activity and leads to chronic inflammation, often causing pain and difficulty with speaking or eating (131)(134).
2. The disease mechanism behind OLP is complex and includes overactive immune cells, various inflammatory cytokines like IL-1, IL-6, IFN-γ, and the presence of specific microbes such as Fusobacterium nucleatum and Candida albicans (135)(136)(137).
3. Many patients with OLP suffer emotionally, especially from anxiety and depression, due to ongoing pain and appearance-related concerns. These feelings are sometimes made worse by the side effects of the medications used for treatment (121)(122)(125)(126).
4. Management usually focuses on easing symptoms using corticosteroids, immune-modulating drugs, and alternative treatments such as plant-based remedies or physical therapies like lasers (127)(129)(133).
5. Recently, innovative treatments have been gaining attention, including stem cell-based therapy, the use of nano-drugs, and medications that block certain immune signals. These may provide longer-term relief with fewer side effects (128) (130)(132).
6. Because OLP can strongly affect mental and emotional health, it's important to include psychological care in treatment plans, not just physical treatment (122)(138).

4.7. Recommendations for Future Researchers

1. Design wider and more detailed studies on how stem cells and nanotechnology can be used safely and effectively for OLP (128) (132).
2. Evaluate the benefits and risks of natural and non-drug treatments for long-term use (133)(127).

3. Look deeper into how oral bacteria influence the development of OLP, and consider them as new treatment targets (135) (136).
4. Encourage the addition of mental health assessments and support as part of OLP research and patient care strategies (121) (122).

Chapter Five

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الخلاصة

المقدمة

الحزاز المسطح الفموي ((OLPهو حالة التهابية مزمنة تصيب الغشاء المخاطي للفم، وتتميز باضطرابات مناعية وأسباب متعددة العوامل. تستكشف هذه الدراسة الأساس النظري للآليات المناعية والتفاعلات الميكروبية التي تساهم في إمراضية الحزاز المسطح الفموي.

المنهجية

استُخدم نهج نوعي قائم على الدراسات، مع التركيز على البيانات التي خضعت لمراجعة الأقران والمتعلقة بنشاط السيتوكينات، وديناميكيات الخلايا المناعية، والارتباطات النفسية. لم تُجرَ أي تجارب سريرية أو معملية في هذا البحث.

النتائج

تشير النتائج إلى دور بارز للسيتوكينات المؤيدة للالتهابات وأنواع ميكروبية محددة في استمرارية الحزاز المسطح الفموي. بالإضافة إلى ذلك، يبدو أن للتوتر النفسي تأثيرًا محتملًا على تكرار الأعراض وشدتها.

المناقشة

تُبرز مناقشة البيانات تعقيد التفاعل المناعي والميكروبي في الحزاز المسطح الفموي، وتُؤكد على الحاجة إلى استراتيجيات علاجية تكاملية. قد تستفيد التوجهات المستقبلية من استكشاف علاجات غير تقليدية تستهدف العوامل البيولوجية والنفسية.

الكلمات المفتاحية: الحزاز المسطح الفموي، الاستجابة المناعية، السيتوكينات، التورط الميكروبي، العلاج التجديدي.

جمهورية العراق
وزارة التعليم العالي والبحث العلم
جامعة ميسان
كلية طب الأسنان

العنوان

دور المناعة الذاتية في حدوث الحزاز المسطح الفموي: مراجعة منهجية

مشروع تخرج مقدم إلى قسم طب الأسنان استكمالاً لمتطلبات نيل درجة البكالوريوس في علوم طب الأسنان

بإشراف:

م. د. أحمد محمد علوان

إعداد الطلبة:

أم البنين ناصر رسن

زينب حسن عبد الله

2025