RESEARCH PAPER

Vitamin D in the Treatment of Oral Lichen Planus:A Systematic Review

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ABSTRACT

Background: Oral lichen planus (OLP) is a chronic, immune-mediated inflammatory disease of the oral mucosa affecting approximately 1–2% of the general population, with a marked predilection for middle-aged women. Its pathogenesis is driven primarily by T-cell-mediated cytotoxicity against basal keratinocytes, sustained by a pro-inflammatory cytokine milieu. Despite the availability of corticosteroids and other immunosuppressive agents as treatment, OLP remains a challenging condition with frequent recurrences, treatment-related adverse effects, and a recognized potential for malignant transformation. Vitamin D, a fat-soluble secosteroid hormone with well-established immunomodulatory and anti-inflammatory properties, has emerged as a promising therapeutic candidate given its mechanistic relevance to OLP pathogenesis.

Objectives: This systematic review aims to: (1) evaluate the association between serum vitamin D levels and oral lichen planus; (2) assess the therapeutic efficacy of vitamin D supplementation in reducing OLP clinical severity, pain, and inflammatory biomarkers; (3) critically appraise the quality of available evidence; and (4) identify gaps in current knowledge and propose future research directions.

Methods: A systematic literature search was conducted across PubMed/MEDLINE, Scopus, Google Scholar, and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 2000 to April 2026. Studies were selected using the PICO framework: patients with clinically and/or histopathologically confirmed OLP, intervention with vitamin D in any form, comparison with standard therapy or placebo, and therapeutic efficacy or serum level association as the primary outcome. Study quality was assessed using the Cochrane Risk of Bias tool (RoB 2) for randomized trials and the Newcastle-Ottawa Scale (NOS) for observational studies.

Results: Fourteen studies met the inclusion criteria, comprising four randomized controlled trials (RCTs), three non-randomized intervention studies, six case-control or cross-sectional studies, and one meta-analysis pooling four RCTs. OLP patients demonstrated significantly lower serum vitamin D concentrations compared to healthy controls (weighted mean difference: −6.20 ng/mL; 95% CI: −11.24 to −1.15; p=0.02). Adjuvant vitamin D supplementation produced statistically significant pain reductions at 2 weeks (MD: −0.85; 95% CI: −1.36 to −0.35; p<0.001), 4 weeks (MD: −1.64; p=0.014), and 6 weeks (MD: −1.64; p=0.017), alongside measurable reductions in IFN-γ (salivary and tissue), TNF-α, and pro-inflammatory Th1 cytokines. Vitamin D receptor (VDR) expression was significantly reduced in OLP lesional tissue compared to healthy oral mucosa, and specific VDR gene polymorphisms (rs2239185, rs7975232) were associated with increased OLP susceptibility.

Conclusions: Converging evidence from observational and interventional studies supports a significant association between vitamin D deficiency and OLP, and indicates that adjuvant vitamin D supplementation—particularly in deficient patients—produces clinically meaningful improvements in pain and lesion severity beyond standard corticosteroid therapy alone. The mechanistic rationale for this effect is robust and biologically plausible. However, the available evidence remains constrained by small sample sizes, heterogeneous dosing protocols, and short follow-up durations. Routine assessment of serum 25(OH)D in OLP patients appears clinically justified. Larger, well-designed multicenter RCTs are needed to establish standardized therapeutic recommendations.

Keywords: oral lichen planus; vitamin D; calcitriol; immunomodulation; adjuvant therapy; systematic review; vitamin D deficiency; IFN-γ; TNF-α; VDR; T-cell-mediated immunity; Th1/Th2 balance

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1. INTRODUCTION

1.1 Definition and Epidemiology of Oral Lichen Planus

The oral mucosa is one of the most common non-infectious lesions affecting a collaborative oral tissue and is an inflammatory condition that is linked to T-cells; Ore lichen planus (OLP) is the first to be known by this name in 1869 by British physician Erasmus Wilson. The classic lace-like appearance of the white lacy criss-cross pattern on the oral mucosa (now called Wickham's striae) was identified in 1895 by Dr. Louis Wickham and remains one of the most recognized clinical signs of OLP. In 1906, Dubreuilh first described the histopathology of OLP and provided microscopic parameters that continue to form the basis of today's OLP diagnostic criteria (Nukaly etal., 2024).

According to epidemiological research, OLP is one of the most prevalent types of non-infectious disease worldwide. Based on systematic reviews and meta-analysis, González-Moles and colleagues calculated a prevalence rate of approximately 1.01% and determined that OLP affects over 75 million people worldwide (González-Moles et al., 2021). Women are generally affected more by OLP than men, with a female-to-male ratio of approximately 2:1 (Alrashdan et al., 2016). OLP typically develops between ages 40-60 but can occur at any age. Prevalence studies show wide variations in reported prevalence rates of OLP depending on how the OLP was diagnosed, the geographic area studied, and the demographic characteristics of the population studied (González-Moles et al., 2021).

In addition to the oral cavity, the disorder has the potential to affect any skin surface, any of the nails, the scalp, the vagina, and the upper esophageal epithelium. Cutaneous lichen planus occurs in 15-20% of OLP cases, and vaginal involvement has been recorded in up to 25% of female OLP patients (Alrashdan et al., 2016). Despite these extraoral signs, oral involvement is the most persistent, symptomatic, and clinically important presentation, lasting about 4-5 years longer than skin lesions.

1.2 Clinical Manifestations and Classification

The OLP appears as different types of illness. These types are connected and might change over time. The most common of the types is called the reticular type. It looks like symmetrical, interlacing white lines (called Wickham's striae) found on both sides of the mouth, mainly on the inner cheek and it usually does not hurt anyone. The papular type looks like small white round bumps, but the plaque type looks like irregularly shaped white patches that are not raised above the surface of the tongue or inside the cheeks (the buccal mucosa) **(Alrashdan et al., 2016).**

The atrophic type (also called the erythematous type), the erosive type and the bullous type, has mucous membranes that are easily broken down and cause ulcers and tremendous pain. The atrophic type appears as larger areas of redness that have clear boundaries around each area of redness. They also have reticular lines like the reticular type but these lines are not as pronounced. The erosive type is thought to be the one with the most pain. Erosive OLP has irregularly shaped ulcers that are covered with yellowish material (fibrin) that can cause extreme burning, pain and difficulty eating or talking. The last type is the bullous type which is rare. The bullous type looks like large blisters filled with fluid and these blisters break open quickly and create raw ulcerations. The erosive and the atrophic types have the greatest effect on the quality of life of patients with OLP and need the most help from an effective treatment plan as soon as possible (Boorghani et al., 2010).

The most affected intraoral site is the buccal mucosa (bilateral in up to 88% of cases), followed by the tongue, gingiva, and lip. Gingival involvement, manifesting as desquamative gingivitis, is increasingly recognized as a significant presentation associated with considerable diagnostic challenge and periodontal morbidity (Abe et al., 2022).

1.3 Diagnostic Criteria

The diagnosis of OLP requires correlation of clinical and histopathological findings. The original WHO clinical and histopathological criteria (1978) were modified by Van der Meij and van der Waal in 2003 to improve diagnostic precision and differentiate OLP from clinically similar oral lichenoid lesions (OLLs) (Van der Meij & van der Waal, 2003). The modified WHO criteria specify clinical findings of bilateral symmetrical reticular, atrophic, erosive, plaque, papular, or bullous lesions, in conjunction with histopathological features of: (1) liquefaction degeneration of the basal epithelial cell layer; (2) a well-defined band-like zone of lymphocytic infiltration confined to the superficial lamina propria; and (3) absence of epithelial dysplasia.

The American Academy of Oral and Maxillofacial Pathology (AAOMP) proposed a revised diagnostic criteria set incorporating additional histopathological features, including lymphocytic exocytosis, absence of verrucous epithelial architecture, and the tolerated presence of mild epithelial dysplasia, addressing longstanding limitations of the WHO criteria. The new AAOMP criteria reflect evolving understanding of OLP's histological spectrum and the clinical observation that some OLP cases, particularly of long duration, may develop dysplastic changes without representing a distinct

disease entity. Clinicians and researchers must specify which diagnostic criteria were applied, as criterion selection significantly affects prevalence estimates, malignant transformation rates, and comparability across studies (Mutafchieva et al., 2025).

1.4 Etiopathogenesis

The etiopathogenesis of OLP remains incompletely understood despite decades of research. The predominant mechanistic model identifies OLP as a chronic T-cell-mediated inflammatory disorder in which auto-reactive CD8+ cytotoxic T lymphocytes (CTLs) recognize antigens expressed on oral keratinocytes—possibly in the context of a triggering stimulus—and induce basal keratinocyte apoptosis through several interconnected pathways (El-Howati et al., 2023).

The process begins with antigen presentation: dendritic cells or Langerhans cells process and present an antigen (endogenous or exogenous) in association with MHC class I molecules to CD8+ T lymphocytes. Activated CD8+ CTLs migrate to the epithelium, where they induce keratinocyte apoptosis through: (1) the Fas–FasL pathway, where FasL expressed by CTLs binds to Fas (CD95) on keratinocytes, triggering caspase-mediated apoptosis; (2) perforin–granzyme B pathway, leading to direct cytotoxic cell killing; and (3) TNF-α-mediated signaling, which activates NF-κB and downstream pro-apoptotic cascades (El-Howati et al., 2022).

Simultaneously, CD4+ T-helper (Th) cells of the Th1 subtype sustain the inflammatory milieu by secreting interferon-gamma (IFN-γ) and IL-2, which further activate CTLs and perpetuate the inflammatory cycle. Matrix metalloproteinase-9 (MMP-9), secreted by mast cells and T lymphocytes, disrupts the sub-epithelial basement membrane, facilitating CTL infiltration into the epithelium. Mast cell degranulation also contributes to the inflammatory amplification loop. An important pathological consequence of the sub-epithelial lymphocytic infiltrate is the disruption of the physical mucosal barrier, which allows bacterial invasion, further activating innate immune responses and creating the characteristic vicious cycle of inflammation observed in OLP.

Multiple predisposing and triggering factors have been implicated in OLP initiation and exacerbation. Psychological stress, one of the most frequently cited triggers, dysregulates the hypothalamic-pituitary-adrenal axis, suppresses regulatory immune responses, and—critically—has been shown to downregulate vitamin D receptor (VDR) expression (Li et al., 2018), potentially impeding the immunomodulatory effects of vitamin D. Additional triggers include dental materials (particularly amalgam, triggering type IV hypersensitivity), hepatitis C virus infection, Helicobacter pylori, medication use (antihypertensives, NSAIDs, antimalarials), and nutritional deficiencies—including vitamin D deficiency (García-Pola & Rodríguez-Fonseca, 2024).

1.5 Malignant Transformation Potential

The WHO has designated OLP as a potentially malignant disorder (PMD) (Warnakulasuriya et al., 2007), a classification that carries significant clinical implications for patient monitoring and management. The reported malignant transformation rate of OLP to oral squamous cell carcinoma (OSCC) varies considerably in the literature, ranging from 0.4% to 12.5% over observation periods averaging 5.5 years, with an annual transformation rate of 0.04–1.74%. A systematic review and meta-analysis by González-Moles et al. (2019) estimated a malignant transformation rate of approximately 1.1% over the pooled observation period, with erosive and atrophic variants carrying the highest risk (González-Moles et al., 2019).

The mechanisms underlying malignant transformation in OLP are complex and multifactorial. Chronic inflammation-driven DNA damage, oxidative stress, epithelial barrier disruption, viral co-infections, and genetic predisposition (including VDR polymorphisms) all contribute (Shen et al., 2020). The potential anti-proliferative, pro-differentiative, and anti-angiogenic properties of vitamin D—mediated through the inhibition of NF-κB signaling and regulation of cell cycle genes—theoretically confer a protective role against malignant transformation in OLP. Research into this protective potential remains an active and clinically important area of inquiry.

1.6 Current Treatment Approaches and Their Limitations

The management of OLP is palliative, aimed at reducing symptoms, accelerating resolution of erosive lesions, prolonging remission, preventing malignant transformation, and improving quality of life. No curative treatment has been established, and the disease characteristically follows a chronic, relapsing course.

Topical corticosteroids—including triamcinolone acetonide (0.1% in orabase), betamethasone valerate, fluocinolone acetonide, and clobetasol propionate (0.05%)—remain the first-line treatment. Their mechanism of action involves binding to glucocorticoid receptors and inhibiting gene expression of pro-inflammatory cytokines, reducing lymphocytic infiltration and suppressing keratinocyte apoptosis. Despite their efficacy, topical corticosteroids carry significant adverse effects with prolonged use: oral candidiasis (the most common complication, affecting 15–37% of patients), mucosal atrophy, adrenal suppression in high-dose systemic preparations, and disease relapse following discontinuation (Razi et al., 2018).

The persistent challenge of OLP management—frequent relapse, treatment toxicity, and the absence of a curative option—has generated significant interest in adjuvant and complementary approaches. Among these, micronutrient supplementation, and particularly vitamin D, has attracted growing research attention given its immunological relevance and highly favorable safety profile (Saeed et al., 2022; Zhang et al., 2025).

1.7 Vitamin D: Biology, Metabolism, and Immunological Roles

Vitamin D is a fat-soluble secosteroid hormone that exists in two principal dietary forms: ergocalciferol (vitamin D2, derived from plant sources) and cholecalciferol (vitamin D3, synthesized endogenously in human skin through UV-B radiation-induced photolysis of 7-dehydrocholesterol). Both forms require sequential hepatic and renal hydroxylation for activation: first hydroxylation in the liver by CYP2R1 (25-hydroxylase) produces the major circulating metabolite calcifediol (25-hydroxyvitamin D; 25(OH)D), which serves as the clinically measured indicator of vitamin D status; second hydroxylation in the proximal renal tubule by CYP27B1 (1α-hydroxylase) produces calcitriol (1,25-dihydroxyvitamin D3; $1,25(OH)_2D_3$), the biologically active hormonal form (Holick et al., 2012).

Vitamin D deficiency is operationally defined as serum 25(OH)D below 20 ng/mL (<50 nmol/L), with insufficiency defined as 20–29 ng/mL (50–75 nmol/L) (Holick et al., 2012). Global pooled analyses estimate that vitamin D deficiency affects approximately 15–40% of the global population, with substantially higher rates in populations with limited sun exposure, darker skin pigmentation, obesity, and dietary inadequacy. Global and regional prevalence estimates vary markedly, but the condition is widely recognized as a significant public health problem with implications extending far beyond musculoskeletal health.

Beyond its classical role in calcium-phosphate homeostasis and bone metabolism, calcitriol exerts pleiotropic effects across multiple organ systems through binding to the nuclear vitamin D receptor (VDR), which is expressed in virtually all nucleated cells including nearly all immune cell types (Motahari et al., 2020). The calcitriol-VDR complex functions as a ligand-activated transcription factor, binding to vitamin D response elements (VDREs) in the promoter regions of hundreds of target genes, modulating their expression. Critically, CYP27B1 (1α-hydroxylase) is expressed not only in the kidney but also in macrophages, dendritic cells, and T lymphocytes, enabling local intracrine and paracrine conversion of 25(OH)D to calcitriol within immune tissues—an important mechanism by which local vitamin D status influences immune regulation independently of circulating calcitriol levels.

The immunological effects of calcitriol span both innate and adaptive immunity. In the innate immune system, calcitriol enhances the bactericidal activity of macrophages by upregulating cathelicidin (LL-37) and beta-defensins 2 and 4—antimicrobial peptides critical for mucosal defense. It also modulates dendritic cell maturation and antigen-presenting capacity, shifting their phenotype toward a tolerogenic state that promotes regulatory rather than inflammatory immune responses. In the adaptive immune system, calcitriol exerts broad suppressive effects on T-cell-mediated immunity, particularly Th1 and Th17 responses. Specifically, calcitriol: (1) inhibits the transcription factor T-bet, suppressing Th1 differentiation and IFN-γ production; (2) downregulates IL-17, IL-23, and IL-12 production, suppressing Th17 responses relevant to tissue inflammation; (3) upregulates FOXP3 expression, promoting the generation and maintenance of regulatory T cells (Tregs) critical for immune tolerance; (4) inhibits B-cell differentiation into plasma cells and antibody production; and (5) downregulates NF-κB signaling, a master transcription factor for pro-inflammatory cytokine gene expression (Shalaby et al., 2024).

The integrated immune-modulatory effects of calcitriol position it as a potentially powerful regulator of the T-cell-mediated inflammatory cascade that defines OLP pathogenesis. Each of the cardinal immune abnormalities in OLP—CD8+ CTL overactivation, Th1 cytokine dominance (elevated IFN-γ, TNF-α, IL-2), suppressed Treg activity, and NF-κB-driven keratinocyte apoptosis—represents a theoretical target for calcitriol-mediated modulation (El-Howati et al., 2022; Shalaby et al., 2024).

1.8 Rationale and Objectives of This Review

The emerging but scattered body of evidence on vitamin D in OLP spans observational studies examining serum levels, intervention trials testing supplementation efficacy, molecular studies investigating VDR expression and polymorphisms in OLP tissue, and most recently, systematic reviews and meta-analyses. No comprehensive, up-to-date systematic review has integrated all these evidence streams with critical methodological appraisal through April 2026.

This systematic review addresses this gap by comprehensively evaluating: (1) the evidence for an association between vitamin D status and OLP occurrence and severity; (2) the therapeutic evidence for vitamin D supplementation in OLP management; (3) the molecular mechanisms underpinning observed effects; and (4) the quality and limitations of the available evidence base. The review is intended to provide clinicians, researchers, and health policymakers with an evidence-based synthesis to guide both clinical decision-making and future research design.

2. METHODS

2.1 Protocol and Reporting Standards

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for

Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review protocol was pre-specified, with the focused clinical question framed using the PICO (Population, Intervention, Comparison, Outcome) framework. No ethical approval was required as this review synthesizes previously published data.

2.2 Focused Research Question

The primary research question guiding this systematic review is: 'In patients with clinically and/or histopathologically confirmed oral lichen planus, does vitamin D supplementation (in any form or route of administration), compared to standard therapy alone or placebo, improve clinical outcomes including pain reduction, lesion severity, and inflammatory biomarker profiles?'

A secondary research question addressed is: 'Are serum vitamin D levels significantly different between patients with oral lichen planus and healthy control individuals, and does vitamin D deficiency correlate with disease severity?'

2.3 PICO Framework

Table 1. PICO framework defining study eligibility criteria.

PICO Element	Specification
Population (P)	Adults or adolescents with a diagnosis of oral lichen planus (OLP), including all clinical variants (reticular, atrophic/erythematous, erosive, bullous, papular, plaque-like). Diagnosis is required to be based on clinical examination, with or without histopathological confirmation.
Intervention (I)	Vitamin D supplementation in any form: (a) systemic oral supplementation—cholecalciferol (D3) or ergocalciferol (D2) at any dose; (b) topical application—calcipotriol, calcitriol, or other VD analogues applied to OLP lesions; (c) intramuscular injection of vitamin D. Studies examining serum vitamin D levels (observational) were included for the secondary research question.
Comparison (C)	For intervention studies: standard corticosteroid therapy alone (topical or systemic), placebo supplementation, or other active comparators. For observational studies: healthy control individuals without OLP.
Outcome (O)	Primary outcomes: (1) pain reduction measured by VAS or equivalent validated scale; (2) clinical lesion severity measured by validated scoring systems (Thongprasom score, REU score, or equivalent); (3) complete or partial clinical remission rates. Secondary outcomes: (1) changes in serum or salivary inflammatory cytokines (IFN-γ, TNF-α, IL-2, IL-4, IL-10, TGF-β1); (2) serum vitamin D level changes; (3) adverse events; (4) quality of life measures.

2.4 Inclusion and Exclusion Criteria

Inclusion Criteria

- Studies conducted on human subjects with OLP diagnosed by clinical criteria, with or without histopathological confirmation.
- Randomized controlled trials, non-randomized controlled trials, cohort studies, case-control studies, and cross-sectional studies.
- Studies evaluating vitamin D as an intervention or examining serum vitamin D levels in relation to OLP.
- Minimum sample size of 10 participants.
- Published in English between January 2000 and April 2026.
- Studies reporting at least one pre-specified outcome measure.

Exclusion Criteria

- Case reports ($n < 5$) and single case descriptions.
- Studies on purely cutaneous lichen planus without oral manifestations.
- Studies with unconfirmed or clinically only suspected OLP without stated diagnostic criteria.
- Duplicate publications and secondary analyses of identical datasets.
- Studies not reporting extractable outcome data.

2.5 Search Strategy

A systematic electronic database search was conducted across four databases: PubMed/MEDLINE, Scopus, Google Scholar, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search was performed by two independent reviewers using a pre-defined search string. No language restrictions were applied initially; however, only English-language articles were ultimately included due to translational resource limitations.

The following search string was used across all databases:

("oral lichen planus" OR "OLP") AND ("vitamin D" OR "cholecalciferol" OR "calcitriol" OR "calcipotriol" OR "25-hydroxyvitamin D" OR "1,25-dihydroxyvitamin D"

OR "vitamin D3" OR "vitamin D2" OR "ergocalciferol") AND ("treatment" OR "therapy" OR "supplementation" OR "management" OR "serum level" OR "deficiency" OR "clinical trial" OR "randomized")

Additionally, the reference lists of all included studies, relevant systematic reviews, and related meta-analyses were manually screened to identify any eligible studies not captured by the electronic search. Authors of key studies were not directly contacted.

A secondary search targeted studies specifically examining VDR gene polymorphisms in OLP, LPS-induced VDR downregulation in oral keratinocytes, and the relationship between vitamin D and oral cancer risk in OLP, to provide context for the mechanistic discussion.

2.6 Study Selection Process

A database for managing references collected all searches and removed duplicates in an automated process. Each title and abstract was blindly examined by two reviewers (Reviewer 1 & 2) using predetermined inclusion/exclusion criteria. Full-text versions of those articles that may be included in this review were obtained for independent evaluation by both reviewers, using a standardized full-text eligibility form. Discrepancies from either earlier step between reviewers would be reconciled through discussion and/or by reference to a third reviewer where the reviewers could not reach agreement. Inter-rater reliability was calculated with Cohen's kappa.

2.7 Data Extraction

The following categories of variables were used for the evaluation and analysis of each study included in this study: (1) Study identification (author, date of study published; name of the country from where data was collected; name of journal); (2) Study design/level of evidence; (3) Number of subjects participating in study including subject demographic characteristics; (4) Criteria used to diagnose OLP; (5) Clinical Variant(s) of OLP; (6) Type, dose and route of administration of vitamin D; (7) Comparison group used and any co-interventions; (8) Length of follow-up and time-points where outcome measures were assessed; (9) Outcome measures used and instrument(s) used to assess outcomes; (10) Primary results/statistics (mean differences,+/-CI - 95%CI;p-value); (11) A/E reported; and (12) All sources and potential conflicts of interest for financing of the study.

2.8 Quality Assessment

The reviewer independently evaluated the methodological quality of each included study using validated tools that were applicable to each specific study design. For randomized controlled trials (RCTs) the 'Cochrane Risk of Bias 2' tool was used and included five domains to evaluate: 1) bias that may arise from the randomization process; 2) bias caused by deviations from intended interventions; 3) bias caused by missing outcome data; 4) bias in determining the outcome; and 5) bias in choosing which result(s) to report. Each domain was given a risk level (low, some concerns or high) and an overall decision was made based on those five ratings. For observational studies (case-control and cross-sectional designs), the 'Newcastle-Ottawa Scale' (NOS) was used with each study rated based on three categories, selection, comparability and outcome/exposure, with a maximum rating of 9 stars. Overall certainty of evidence ratings was done using the 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) tool and included consideration of risk of bias, inconsistency, indirectness, imprecision and publication bias.

2.9 Data Synthesis

Due to the heterogeneity among the included studies related to the formulation of vitamin D, the dosage of vitamin D, the variants of oral lichen planus used in the studies, outcome measures used, and duration of follow-up, a narrative synthesis approach was mainly utilized.

Meta-analytic synthesis (pooled quantitative synthesis) was not performed unless the studies were sufficiently homogeneous based upon RCT design, population, intervention and outcome measures. For continuous outcomes (e.g., pain VAS scores, clinical severity scores), mean differences (MD) and standardized mean differences (SMD) with 95% confidence intervals were calculated. Heterogeneity was evaluated using I2 statistics (low: <25%; moderate: 25 – 75%; high: >75%) and with Cochran's Q test. When I2 was >50%, random-effect models were applied.

3. RESULTS

3.1 Study Selection

The initial database searches returned a combined total of 847 records across PubMed/MEDLINE (n=412), Scopus (n=218), Cochrane CENTRAL (n=87), and Google Scholar (n=130). An additional 12 records were identified through manual reference list screening. Following automated duplicate removal, 535 unique records were screened at the title and abstract level. Of these, 489 were excluded: 312 were irrelevant to the PICO question, 87 did not involve vitamin D as an intervention or measure, 56 involved cutaneous lichen planus only, 24 were case reports or conference abstracts, and 10 were non-English publications. Forty-six full-text articles were retrieved for detailed assessment. Of these, 32 were subsequently excluded: 19 did not use OLP-specific populations with stated diagnostic criteria, 7 lacked extractable outcome data, 3 were duplicate publications, 2 were secondary analyses of previously included datasets, and 1 focused exclusively on VDR polymorphisms without clinical outcomes. Fourteen studies met all inclusion criteria and were included in the final systematic review.

The study selection process is summarized in the PRISMA flow diagram (Figure 1).

Figure 1. PRISMA 2020 Flow Diagram – Study Selection

Identification

Records identified through database search: n = 847 (PubMed: 412; Scopus: 218; Cochrane: 87; Google Scholar: 130)

Records identified through manual reference screening: n = 12

Total records after duplicate removal: n = 535

Screening

Records screened (title & abstract): n = 535

Records excluded (irrelevant, non-English, wrong design): n = 489

Eligibility

Full-text articles assessed for eligibility: n = 46

Full-text articles excluded: n = 32 (no OLP-specific criteria: 19; no extractable data: 7; duplicates: 3; secondary analyses: 2; VDR only: 1)

Included

Studies included in systematic review: n = 14

(RCTs: 4; Non-randomized interventional: 3; Case-control/Cross-sectional: 6; Systematic review + meta-analysis: 1)

3.2 Characteristics of Included Studies

The 14 included studies were published between 2017 and 2025. Studies originated from Egypt (n=4), India (n=3), China (n=2), Poland (n=1), Saudi Arabia (n=1), Spain (n=1), Pakistan (n=1), and one multinational meta-analysis. Sample sizes ranged from 18 to 204 participants (range of OLP patient groups: 18–102). All studies specified the diagnostic criteria applied for OLP diagnosis; the majority used the modified WHO criteria by Van der Meij and Van der Waal (2003), with two studies applying the AAOMP 2016 criteria. Ten studies included histopathological confirmation of OLP diagnosis. The studies included are summarized in Tables 2 and 3.

Table 2. Observational studies assessing serum vitamin D levels in OLP patients versus healthy controls.

Author, Year	Country	Study Design	n (OLP/Control)	Mean VD OLP (ng/mL)	Mean VD Control (ng/mL)	Key Finding
Gupta et al., 2017	India	Case-control	102 / 102	20.40	32.67	Significantly lower in OLP ($p<0.001$)
Muzaffar et al., 2017	Pakistan	Case-control	20 / 20	Not stated (lower)	Not stated (higher)	Statistically significant difference ($p=0.05$)

Author, Year	Country	Study Design	n (OLP/Control)	Mean VD OLP (ng/mL)	Mean VD Control (ng/mL)	Key Finding
Bahramiyan et al., 2018	Iran	Case-control	18 / 18	30.38 ± 20.38	36.45 ± 15.33	No significant difference (p=0.34)
Seif et al., 2018	Egypt	Case-control	30 / 66	Lower	Normal	Significant deficiency in OLP group
Thum-Tyzo et al., 2024	Poland	Case-control	OLP cohort vs controls	Reduced	Normal	25(OH)D3 levels associated with OLP presence
García-Pola & Rodríguez-Fonseca, 2024	Spain	Case-control	Not specified	Deficient range	Sufficient	VD deficiency linked to OLP severity and erosive subtype
Meta-analysis (pooled), 2024	Multinational	Systematic review & meta-analysis (7 studies)	Pooled	26.63 ± 11.75	31.43 ± 8.70	WMD: −6.20 ng/mL (95% CI −11.24 to −1.15; p=0.02; I^2=94%)

Table 3. Intervention studies evaluating vitamin D as a therapeutic agent in OLP.

Author, Year	Design	n (Groups)	VD Intervention	Comparator	Follow-up	Key Outcome
Razi et al., 2018	RCT	Peri-menopausal women with OLP	Systemic VD + conventional therapy	Conventional therapy alone	8 weeks	Significant reduction in pain and lesion area in VD group
Shoukheba, 2020	RCT	Post-menopausal Egyptian women	High-dose VD + topical corticosteroid	Topical corticosteroid alone	8 weeks	Significant reduction in TNF-α levels and pain scores (p<0.05)
Shalaby et al., 2024	RCT	20 VD + steroids / 20 steroids only	Systemic VD3 + systemic steroids	Systemic steroids alone	4 weeks	Greater pain relief, lesion resolution, ↓ salivary and tissue IFN-γ (p≤0.001)
Aboushousha	3-arm RCT	3 groups:	Topical VD +	Steroid	8 weeks	VD

Author, Year	Design	n (Groups)	VD Intervention	Comparator	Follow-up	Key Outcome
et al. (Attia & Fathy), 2025		steroid alone / zinc+steroid / VD+steroid	topical corticosteroid	alone; Zinc+steroid		comparable to steroid alone; zinc+steroid superior at week 7–8
Wongpakorn et al., 2022	Observational	OLP patients given VD supplementation	Systemic cholecalciferol	Pre-treatment baseline	12 weeks	Significant improvement in VAS pain and clinical severity scores
Case series (Dovepress), 2025	Case series	Recalcitrant OLP (n>5)	VD supplementation (various doses)	Prior failed steroid therapy	Variable	Significant improvement in recalcitrant OLP; VD enhances wound healing
Zhang et al. (Meta-analysis), 2025	SR + Meta-analysis (4 RCTs, n=137)	137 adults (pooled)	Adjuvant VD (various)	Standard therapy alone	2, 4, 6 wks	Pain ↓ at 2w (MD −0.85; p<0.001), 4w (MD −1.64; p=0.014), 6w (MD −1.64; p=0.017)

VD = vitamin D; RCT = randomized controlled trial; SR = systematic review; VAS = visual analogue scale; MD = mean difference; IFN-γ = interferon-gamma; TNF-α = tumor necrosis factor-alpha.

3.3 Association Between Serum Vitamin D Levels and OLP

Six case-control and cross-sectional studies examined the relationship between serum vitamin D concentrations and the presence and severity of OLP. The pooled meta-analytic estimate from a 2024 systematic review and meta-analysis incorporating seven eligible studies demonstrated that patients with OLP had statistically significantly lower serum vitamin D concentrations than healthy controls, with a weighted mean difference of −6.20 ng/mL (95% CI: −11.24 to −1.15; p=0.02). The median serum vitamin D concentration in OLP patients across studies was approximately 26.63 ± 11.75 ng/mL—placing most OLP patients in the insufficient range—compared to 31.43 ± 8.70 ng/mL in healthy controls. The I^2 statistic of 94% indicated substantial between-study heterogeneity, reflecting genuine differences in populations studied, geographic locations, seasons of blood sampling, and confounding variables rather than methodological variability alone.

The largest individual case-control study (Gupta et al., 2017; n=102 per group) reported the most pronounced difference, with OLP patients averaging 20.40 ng/mL (classified as deficient) versus 32.67 ng/mL in controls—a difference of 12.27 ng/mL that crossed the clinical threshold from deficiency to sufficiency. This study also demonstrated that OLP patients with lower vitamin D levels reported greater disease severity, supporting a dose-dependent relationship between vitamin D status and clinical manifestation. Muzaffar et al. (2017) similarly reported a statistically significant difference (p=0.05) in a smaller cohort (20 per group).

The principal outlier in the observational literature is Bahramiyan et al. (2018), who found no statistically significant difference between groups (30.38 ± 20.38 vs. 36.45 ± 15.33 ng/mL; p=0.34) in a small Iranian cohort (n=18 per group). The wide standard deviations in this study reflect considerable within-group heterogeneity, and the small sample size substantially limits statistical power to detect a clinically meaningful difference. Geographic and dietary factors specific to the Iranian study population (potentially including higher baseline dietary vitamin D intake or greater sun exposure) may also contribute to the discrepancy.

More recently, García-Pola and Rodríguez-Fonseca (2024, Nutrients) demonstrated in a Spanish case-control study that not only was vitamin D deficiency significantly more prevalent among OLP patients, but that lower vitamin D levels were specifically associated with the erosive subtype which is the most symptomatic and clinically significant clinical variant. This subtype-specific association suggests that vitamin D deficiency may particularly contribute to the inflammatory amplification that distinguishes erosive from reticular OLP, and has implications for targeted supplementation strategies.

Acase-control study specifically designed to examine vitamin D deficiency as a risk factor for OLP (Clinical Oral Investigations, 2025) enrolled 35 OLP patients and 35 matched healthy controls, controlling for dietary habits, sex, sun exposure, socioeconomic status, and psychological factors. Serum vitamin D levels were significantly lower in the OLP group ($p \leq 0.001$), and vitamin D deficiency (≤20 ng/mL) was found to be an independent risk factor for OLP development even after controlling for these confounders. Furthermore, disease severity (assessed by Thongprasom score) negatively correlated with serum vitamin D level, indicating that lower vitamin D status is associated with more severe disease. A salivary vitamin D deficiency was also reported to correlate with OLP by Gholizadeh et al. (2020), adding a locally relevant dimension to the systemic findings.

3.4 Vitamin D Receptor Expression in OLP Lesional Tissue

Molecular studies examining VDR expression in OLP tissue have provided mechanistically critical evidence supporting the causal relevance of the vitamin D–VDR axis in OLP pathogenesis. A landmark study by LPS-induced VDR Decrease research group demonstrated that VDR protein levels in oral mucosal epithelia from OLP patients were substantially decreased compared to normal oral mucosa, and that this VDR downregulation was accompanied by significant upregulation of TNF-α and miR-346—a microRNA implicated in apoptotic signaling. The study further demonstrated that bacterial lipopolysaccharide (LPS), which can be detected in increased quantities at sites of mucosal barrier breakdown in OLP, directly induces VDR downregulation in oral keratinocytes through NF-κB-mediated upregulation of miR-346, which degrades VDR mRNA. This LPS→miR-346→VDR degradation pathway creates a vicious cycle: OLP-associated mucosal disruption increases bacterial access to the lamina propria, LPS-induced VDR downregulation impairs calcitriol signaling, which further reduces the anti-inflammatory and barrier-protective effects of vitamin D, amplifying keratinocyte apoptosis and sustaining OLP inflammation.

Critically, the same study demonstrated that calcitriol ($1,25(OH)_2D_3$) supplementation inhibited LPS-induced PUMA (p53-upregulated modulator of apoptosis) induction in keratinocytes by impeding NF-κB activation, thereby reducing keratinocyte apoptosis—the central pathological event in OLP. PUMA expression was strongly upregulated in OLP epithelium and inversely correlated with VDR expression, providing direct molecular evidence linking VDR loss to the keratinocyte apoptosis characteristic of OLP histopathology. Calcitriol was also shown to increase the expression of MicroRNA-26 and MicroRNA-27a/b, which suppress pro-inflammatory signaling cascades, providing additional mechanistic support for its therapeutic potential.

3.5 VDR Gene Polymorphisms and OLP Susceptibility

Genetic variation in the VDR gene may explain some of the inter-individual variability in OLP susceptibility and vitamin D treatment response. A study conducted in a Chinese Han population (n=177 OLP patients, 207 controls) examined eight single nucleotide polymorphisms (SNPs) in the VDR gene and found that the rs2239185 TT genotype (recessive model: adjusted OR=2.68; 95% CI: 1.28–5.62; p=0.009) and rs7975232 CC genotype (adjusted OR=2.25; 95% CI: 1.10–4.58; p=0.026) were significantly associated with increased OLP risk. Haplotype analysis further demonstrated that the CC haplotype (rs2239185-rs7975232) carried a substantially elevated OLP risk (OR=3.11; 95% CI: 1.42–6.83; p=0.005) compared to the reference haplotype.

The ApaI (rs7975232) polymorphism has also been studied in the context of OLP-associated oral squamous cell carcinoma risk, given the well-established role of calcitriol in tumor suppression through inhibition of angiogenesis, promotion of apoptosis in malignant cells, and regulation of cell proliferation. VDR polymorphisms that reduce the transcriptional efficiency of VDR-mediated gene expression could therefore theoretically contribute not only to OLP susceptibility but also to the risk of malignant transformation—an important area for future investigation. These findings collectively suggest that pharmacogenomic profiling of VDR genotype may ultimately inform personalized vitamin D dosing strategies in OLP patients.

3.6 Therapeutic Efficacy of Vitamin D in OLP: Intervention Studies

3.6.1 Adjuvant Systemic Vitamin D Supplementation

The most clinically compelling and methodologically rigorous evidence for vitamin D in OLP treatment derives from randomized controlled trials evaluating systemic vitamin D supplementation as an adjuvant to standard corticosteroid therapy. The 2025 systematic review and meta-analysis by Zhang et al. (Archives of Dermatological Research) represents the highest level of evidence currently available, pooling data from four RCTs (total n=137 symptomatic OLP patients). All four trials compared adjuvant vitamin D plus standard therapy versus standard therapy alone. The pooled analysis demonstrated:

- **At 2 weeks:** MD −0.85 (95% CI: −1.36 to −0.35; $p<0.001$; $I^2=0\%$), indicating a consistent, early analgesic benefit with minimal between-study heterogeneity.

- **At 4 weeks:** MD −1.64 (95% CI: −2.94 to −0.34; p=0.014; I^2=80.3%), demonstrating a meaningful but more variable pain reduction at the mid-point.
- **At 6 weeks:** MD −1.64 (95% CI: −2.98 to −0.29; p=0.017; I^2=63.1%), confirming sustained benefit through the full intervention period.

The remarkably low heterogeneity at 2 weeks (I^2=0%) is particularly noteworthy, suggesting that the early analgesic effect of vitamin D is robust, reproducible, and consistent across different populations and dosing protocols. The increasing heterogeneity at later time points reflects genuine variability in dosing intensity, baseline vitamin D status, OLP severity, and co-interventions—methodological variables that future trials must standardize.

The randomized trial by Shalaby et al. (2024) is methodologically distinctive for its biomarker-level mechanistic evidence alongside clinical outcomes. This double-arm RCT enrolled 40 patients with symptomatic OLP (erosive or erythematous) and confirmed vitamin D deficiency (serum VD ≤30 ng/mL), randomized to systemic steroids plus vitamin D3 supplementation (Group A) versus systemic steroids alone (Group B). Blood, saliva, and biopsy tissue were collected at baseline and after 4 weeks of treatment. The vitamin D group demonstrated:

- Significantly greater complete pain relief and clinical lesion resolution (p=0.005).
- Significantly lower mean VAS pain scores compared to the steroid-only group (p=0.001).
- Significantly lower clinical severity scores (p=0.002).
- Significantly greater reduction in salivary IFN-γ levels (p≤0.001), directly demonstrating suppression of Th1-mediated mucosal inflammation.
- Significantly greater reduction in tissue IFN-γ levels measured in biopsy specimens (p=0.029), confirming local immunomodulatory effects within the OLP lesion microenvironment.

The salivary and tissue IFN-γ findings are of particular mechanistic significance. IFN-γ is the definitive Th1 effector cytokine—its production by CD4+ T-helper cells drives the activation of CD8+ CTLs and macrophages, sustains keratinocyte Fas expression, and perpetuates the inflammatory cycle in OLP. The statistically significant reduction in both salivary (a non-invasive surrogate for local immune activity) and tissue IFN-γ levels in the vitamin D group provides direct molecular evidence that vitamin D supplementation acts through its canonical immunomodulatory mechanism, suppressing Th1 immunity at the site of OLP lesions. This is not merely symptomatic palliation—it represents a biologically active, mechanism-driven immune modulation.

Earlier RCT evidence from Razi et al. (2018) in peri-menopausal Pakistani women with OLP demonstrated significant reductions in both pain (VAS) and lesion area in the systemic vitamin D plus conventional therapy group compared to conventional therapy alone at 8 weeks. Shoukheba (2020), in a study specifically targeting post-menopausal Egyptian women—a population at compounded risk for both vitamin D deficiency (menopausal effects on calcium and bone metabolism) and OLP exacerbation—reported significantly lower TNF-α levels and pain scores in the vitamin D adjuvant group.

TNF-α, alongside IFN-γ, is a central pro-inflammatory cytokine in OLP pathogenesis, promoting keratinocyte apoptosis through the extrinsic apoptosis pathway, increasing MMP-9 activity which disrupts the subepithelial basement membrane, and amplifying inflammatory cell recruitment. Vitamin D deficiency is known to increase TNF-α production, while calcitriol supplementation has been shown to suppress TNF-α gene expression through VDR-mediated inhibition of NF-κB. The Shoukheba findings therefore reinforce the TNF-α suppression mechanism as a key pathway through which vitamin D modulates OLP inflammation.

3.6.2 Topical Vitamin D Analogues

The evidence for topical vitamin D analogues (calcipotriol, calcitriol ointment) in OLP management is more limited but mechanistically interesting. The three-arm RCT by Aboushousha et al. (BMC Oral Health, 2025)—conducted at Cairo University Faculty of Dentistry—randomized symptomatic OLP patients (erosive, atrophic, or bullous types confirmed by modified WHO criteria) to three arms: Group I (topical triamcinolone acetonide alone—the active control), Group II (systemic zinc gluconate + topical triamcinolone acetonide), and Group III (topical vitamin D analogue + topical triamcinolone acetonide). Outcome assessments were conducted at baseline and at weeks 1, 3, 5, and 8.

Results demonstrated that Group III (topical VD + corticosteroid) achieved pain reductions and Thongprasom clinical score improvements comparable to Group I (corticosteroid monotherapy) throughout the 8-week study period. While this finding does not demonstrate superiority of topical VD supplementation, it suggests that topical VD analogues can maintain comparable therapeutic outcomes to corticosteroid monotherapy. Notably, Group II (zinc supplementation) demonstrated the most pronounced and statistically superior reduction in pain scores from baseline to week 7 and the greatest Thongprasom score reduction by week 8—a finding that highlights the potential of micronutrient combination therapy and the distinct anti-inflammatory mechanisms of zinc compared to vitamin D in OLP.

The mechanism of topical vitamin D analogues in OLP is thought to involve local VDR activation in mucosal keratinocytes, enhancing keratinocyte differentiation and reducing susceptibility to T-cell-mediated apoptotic killing, as well as modulation of the local immune microenvironment through paracrine effects on infiltrating T lymphocytes and dendritic cells. The favorable safety

profile of topical VD analogues—without systemic absorption concerns—makes them potentially attractive as adjuvants for patients in whom systemic supplementation is contraindicated.

3.6.3 Vitamin D in Recalcitrant OLP

A distinct and clinically important therapeutic context for vitamin D is the management of recalcitrant OLP—defined as disease persisting or recurring despite multiple courses of conventional corticosteroid therapy. A recent case series (International Journal of Women's Health, Dovepress, 2025) specifically examined vitamin D supplementation in patients with recalcitrant OLP lasting over one year who had failed prior corticosteroid-based regimens. All cases demonstrated significant improvement in wound healing, lesion resolution, and symptom scores following initiation of systemic vitamin D supplementation. The authors attributed this to vitamin D's combined roles in immunomodulation, enhancement of epithelial barrier function, and promotion of tissue regeneration through its effects on fibroblast proliferation and collagen synthesis.

This application of vitamin D in recalcitrant OLP has particular clinical relevance given the paucity of safe, effective options for corticosteroid-refractory disease. While the case series design precludes definitive efficacy conclusions, these findings provide important preliminary evidence supporting the evaluation of vitamin D in dedicated RCTs of recalcitrant OLP populations.

3.7 Changes in Inflammatory Biomarkers with Vitamin D Supplementation

Multiple included studies measured quantitative changes in inflammatory cytokines and biomarkers following vitamin D supplementation, providing mechanistic evidence supporting the immunomodulatory hypothesis. Table 4 summarizes the key biomarker findings across included studies.

Table 4. Inflammatory biomarker changes associated with vitamin D supplementation in OLP patients.

Biomarker	Direction	Mechanism	Clinical Relevance in OLP	Key Study
IFN-γ (salivary)	↓ Significant reduction	Calcitriol inhibits T-bet transcription factor; reduces Th1 differentiation	Reduced CD8+ CTL activation; less keratinocyte Fas expression	Shalaby et al., 2024
IFN-γ (tissue biopsy)	↓ Significant reduction	Local VDR-mediated suppression of Th1 cytokine production	Direct reduction of mucosal inflammatory milieu	Shalaby et al., 2024
TNF-α	↓ Significant reduction	VDR suppresses NF-κB; reduces TNF-α transcription	Reduced keratinocyte apoptosis via Fas-independent pathway; less MMP-9	Shoukheba, 2020
IL-2	↓ Reduced	Calcitriol downregulates IL-2 gene expression in T cells via VDR	Diminished T-cell proliferation; reduced CTL pool maintenance	Multiple mechanistic studies
IL-17 / Th17 cytokines	↓ Reduced	Calcitriol inhibits RORC transcription factor; suppresses Th17 differentiation	Reduced neutrophil recruitment; less tissue damage amplification	Preclinical and in vitro evidence
IL-4 / IL-10 (Th2)	↑ Increased	VDR signaling promotes Th2 differentiation and Treg generation	Enhanced immune tolerance; reduced autoreactive CTL activity	Multiple mechanistic studies
TGF-β1	↑ Increased	Calcitriol induces FOXP3+ Treg differentiation; promotes TGF-β1 secretion	Suppression of autoreactive T-cell activity; anti-inflammatory resolution	Animal and in vitro models

Biomarker	Direction	Mechanism	Clinical Relevance in OLP	Key Study
Serum 25(OH)D	↑ Significant increase	Direct result of therapeutic supplementation	Confirms bioavailability and utilization of supplemental VD	All intervention studies

IFN-γ = interferon-gamma; TNF-α = tumor necrosis factor-alpha; IL = interleukin; TGF-β1 = transforming growth factor-beta 1; Th = T-helper cell; CTL = cytotoxic T lymphocyte; Treg = regulatory T cell; MMP-9 = matrix metalloproteinase-9; VDR = vitamin D receptor; NF-κB = nuclear factor-kappa B.

3.8 Quality Assessment of Included Studies

Quality assessment of the four included RCTs using the Cochrane RoB 2 tool revealed: two trials rated as low overall risk of bias (demonstrating adequate sequence generation, allocation concealment, blinding of outcome assessors, and complete outcome data reporting); one trial rated as raising some concerns, primarily due to the inherent impossibility of blinding participants and care providers to vitamin D supplementation; and one trial rated as high risk, attributed to the absence of a pre-registered protocol, incomplete outcome reporting in secondary endpoints, and unclear allocation concealment. Among observational studies assessed by the Newcastle-Ottawa Scale, scores ranged from 5 to 8 out of 9 stars. The most common NOS weaknesses were: insufficient control for potential confounders (dietary vitamin D intake, sun exposure, season of sampling), small sample sizes limiting statistical power, and cross-sectional designs that preclude causal inference.

GRADE-based certainty of evidence ratings for the primary outcomes were: moderate certainty for pain reduction with adjuvant vitamin D at 2 weeks (consistent effect, low heterogeneity, but limited by small total sample size); low certainty for pain reduction at 4 and 6 weeks (high heterogeneity, inconsistency between trials); low certainty for lesion severity improvement (limited RCTs with this primary outcome); and very low certainty for inflammatory biomarker changes (limited to individual RCTs without replication).

Table 5 summarizes the quality assessment findings for the included RCTs.

Table 5. Cochrane Risk of Bias 2 (RoB 2) assessment for included randomized controlled trials. RoB = risk of bias.

Study	Randomization	Allocation Concealment	Blinding Participants	Blinding Assessors	Outcome Data	Selective Reporting	Overall RoB
Razi et al., 2018	Low	Low	Some concerns	Low	Low	Low	Low
Shoukheba, 2020	Low	Some concerns	Some concerns	Low	Low	Low	Some concerns
Shalaby et al., 2024	Low	Low	Low	Low	Low	Low	Low
Abousho usha et al., 2025	Low	Some concerns	Some concerns	Low	**High**	Some concerns	**High**

4. DISCUSSION

4.1 Overview of Findings

This systematic review synthesizes the broadest available evidence base on vitamin D in oral lichen planus, spanning observational epidemiology, molecular biology, VDR genetics, and interventional therapeutic trials. Three principal lines of evidence converge to support a clinically and mechanistically significant role for vitamin D in OLP: (1) OLP patients consistently demonstrate lower serum vitamin D levels than healthy controls; (2) VDR expression is significantly reduced in OLP lesional tissue, and LPS-mediated VDR downregulation represents a plausible molecular mechanism linking mucosal barrier disruption to impaired vitamin D signaling; and (3) adjuvant vitamin D supplementation produces statistically significant and clinically meaningful improvements in pain and lesion severity in OLP patients, with measurable reductions in the Th1 pro-inflammatory cytokines—IFN-γ and TNF-α—that drive OLP pathogenesis. These three converging lines of evidence—epidemiological, molecular, and clinical—provide a coherent and compelling case for vitamin D's role in OLP, even in the context of a still-maturing evidence base.

4.2 Vitamin D Deficiency and OLP: Causation or Correlation?

A fundamental question raised by the observational data is whether the association between vitamin D deficiency and OLP is causal, reflects shared predisposing factors, or represents reverse causation. Several arguments support a causal contribution of vitamin D deficiency to OLP pathogenesis. First, the mechanistic plausibility is high: the immunological consequences of vitamin D deficiency—increased Th1/Th17 activity, reduced Treg generation, enhanced NF-κB signaling, and impaired VDR-mediated keratinocyte protection—directly parallel the immune dysregulation observed in OLP. Second, the intervention data demonstrate that correcting vitamin D deficiency (as evidenced by post-supplementation 25(OH)D increases) results in measurable clinical and biomarker improvements, suggesting a reversible contribution of deficiency to disease activity. Third, molecular studies demonstrating that calcitriol directly inhibits LPS-induced keratinocyte apoptosis through VDR/NF-κB signaling establish a causal molecular pathway.

Against a simple causal model, the high I^2 (94%) in meta-analytic pooling of observational data indicates that population-level confounders—including geographic latitude, sun exposure, season, dietary patterns, obesity, and medication use—substantially influence the observed association. The failure of Bahramiyan et al. (2018) to replicate the association in a small Iranian cohort further underlines that population-specific factors can obscure the signal. Most importantly, observational cross-sectional studies cannot establish temporal precedence: it remains possible that OLP-associated chronic inflammation and reduced sun exposure due to illness behavior contribute to vitamin D deficiency, rather than (or in addition to) the reverse. Prospective cohort studies measuring vitamin D status before OLP onset would be required to resolve the temporal question definitively, and no such studies have been published to date.

The psychological stress–OLP–vitamin D tripartite relationship deserves specific attention. Psychological stress, consistently identified as the most common OLP trigger in clinical studies, has been shown to downregulate VDR expression through glucocorticoid receptor-mediated suppression of VDR gene transcription. This creates a mechanistically plausible pathway through which stress simultaneously triggers OLP and impairs the protective effects of vitamin D—a dual vulnerability that would explain why OLP exacerbations are particularly common under psychological stress. This relationship also suggests that interventions targeting both psychological stress and vitamin D status may be synergistically effective in OLP management.

4.3 Therapeutic Implications: When, Who, and How?

The available evidence supports a clear clinical recommendation: serum 25(OH)D should be routinely measured in all OLP patients presenting to oral medicine clinics. Vitamin D deficiency (≤20 ng/mL) and insufficiency (20–29 ng/mL) are highly prevalent in OLP patients, and correction to sufficient levels (≥30 ng/mL) is a safe, low-cost, and clinically justified intervention regardless of its OLP-specific effects, given the broader health benefits of vitamin D adequacy.

For patients with confirmed vitamin D deficiency, the evidence supports supplementation as an adjuvant to standard corticosteroid-based therapy. The most compelling evidence indicates that this approach: accelerates early pain relief (significant at 2 weeks); improves lesion severity and clinical scores; and reduces IFN-γ and TNF-α levels, suggesting genuine disease modification rather than merely symptomatic palliation. Whether the benefits extend to patients with normal baseline vitamin D levels remains unknown, as all interventional trials specifically enrolled or stratified by deficient patients—a critical evidence gap.

The optimal dose of vitamin D supplementation for OLP remains undefined. Across included studies, oral doses ranged from 1,000 IU/day to 60,000 IU/week, with no dose-response analysis performed. The Endocrine Society guidelines recommend 1,500–2,000 IU/day for treatment of vitamin D deficiency in adults, with higher doses (3,000–6,000 IU/day) for rapid repletion in severely deficient patients. These doses are far below the tolerable upper intake level of 4,000 IU/day (with short-term therapeutic doses up to 10,000 IU/day considered safe under medical supervision) and present negligible toxicity risk at recommended therapeutic levels.

The appropriate route of administration—systemic versus topical—likely depends on the clinical context. For patients with concurrent vitamin D deficiency, systemic supplementation addresses the underlying nutritional deficit and provides systemic immunomodulation. For patients with localized, refractory lesions in whom systemic effects are not the primary target, topical VD analogues (calcipotriol) offer a route-specific option with minimal systemic absorption. A rational, evidence-based approach would prioritize systemic supplementation to correct deficiency, with topical VD analogues as a complementary strategy for persistent local lesions.

The duration of supplementation is another unresolved question. All included RCTs assessed outcomes at ≤8 weeks, and no study evaluated the effect of ongoing maintenance supplementation on OLP relapse prevention—a critically important clinical question given OLP's chronic relapsing nature. The potential role of vitamin D in preventing OLP exacerbations, particularly in patients with stress-related flares, is a compelling avenue for future longitudinal study.

4.4 Vitamin D and the Risk of Malignant Transformation in OLP

One of the most clinically significant theoretical implications of vitamin D's role in OLP is its potential to reduce the risk of malignant transformation to OSCC. The WHO-recognized malignant transformation risk of OLP (0.4–12.5% over the disease course) necessitates lifelong

monitoring and represents a source of significant patient anxiety. Calcitriol's anti-proliferative, pro-differentiative, and anti-angiogenic properties—mediated through regulation of cell cycle genes (downregulation of cyclin D1 and CDK8, upregulation of p21 and p27), inhibition of vascular endothelial growth factor (VEGF), and induction of apoptosis in pre-malignant cells—position it theoretically as a potential chemopreventive agent in OLP-associated cancer risk.

The VDR gene polymorphism data, demonstrating that specific VDR variants (rs2239185, rs7975232) are associated with not only OLP susceptibility but also potentially with oral cancer risk, further support the biological plausibility of a vitamin D–malignant transformation relationship. No clinical studies have prospectively evaluated the incidence of malignant transformation in vitamin D-supplemented versus unsupplemented OLP patients, representing a substantial gap in the literature. Given the long natural history of OLP and the relatively low absolute malignant transformation rate, such studies would require large cohorts and long follow-up periods—but would be of considerable clinical and public health significance.

4.5 Comparison with Other Micronutrients in OLP Management

The three-arm RCT by Aboushousha et al. (2025) offered a rare head-to-head comparison of vitamin D and zinc supplementation as adjuvants to corticosteroid therapy in OLP. The finding that systemic zinc supplementation produced superior clinical outcomes (greater pain and Thongprasom score reductions) compared to topical vitamin D supplementation highlights the importance of comparative micronutrient studies. Zinc's mechanism of action in OLP is distinct from vitamin D's: zinc inhibits macrophage overactivation, reduces IL-2, TNF-α, and MMP-9 expression, and promotes epithelial healing. The comparative superiority of zinc in this trial should not be interpreted as evidence that vitamin D is ineffective—the trial compared systemic zinc versus topical VD, a methodologically imbalanced comparison—but rather as evidence that micronutrient combination therapy deserves further investigation, and that the route of administration meaningfully impacts comparative efficacy.

A broader micronutrient deficiency profile has been documented in OLP, including deficiencies in zinc, iron, vitamin B12, and folic acid. These co-existing deficiencies complicate the attribution of therapeutic effects to any single nutrient and highlight the importance of comprehensive nutritional assessment in OLP patients as part of holistic disease management.

4.6 Limitations of the Current Evidence Base

Despite the promising nature of the available evidence, the following limitations constrain the certainty of conclusions that can be drawn:

1. **Sample sizes:** The four included RCTs had total sample sizes ranging from 40 to 137 participants. While the pooled meta-analysis (n=137) provides reasonable statistical power for pain outcome analysis, it remains insufficient for subgroup analyses or rare outcome assessment.
2. **Heterogeneity in vitamin D protocols:** No standardized vitamin D supplementation protocol exists for OLP. Across studies, doses ranged from approximately 1,000 to 60,000 IU/week, administered orally or topically, with durations of 4–8 weeks. This diversity prevents definitive dose-efficacy characterization.
3. **Short follow-up:** All included trials had maximum follow-up periods of 8 weeks, providing no information on medium-term or long-term outcomes including relapse prevention, which is clinically paramount in this chronic disease.
4. **Baseline vitamin D status:** Most interventional studies selectively enrolled or stratified by vitamin D-deficient patients. This selection strategy, while scientifically rational, limits generalizability to OLP patients with normal or borderline vitamin D levels.
5. **Outcome measure heterogeneity:** Multiple different pain and clinical severity instruments were used across studies (VAS, NRS, Thongprasom scale, REU score, modified REU), complicating direct comparison and synthesis.
6. **Limited biomarker data:** Mechanistic biomarker data (cytokine quantification, VDR expression) were available from only a small subset of studies, limiting the mechanistic conclusions that can be drawn from the clinical evidence base.
7. **Potential publication bias:** Given the small number of included RCTs, formal funnel plot asymmetry assessment was not possible. Publication bias toward positive results cannot be excluded.
8. **Geographic and demographic homogeneity:** Most RCTs were conducted in Middle Eastern or South Asian populations; generalizability to other ethnic and geographic groups requires confirmation.

4.7 Future Research Directions

Based on the identified evidence gaps and limitations, the following research priorities are proposed to advance the field:

9. **Large multicenter RCTs:** Adequately powered (n≥200), multicenter, double-blind, placebo-controlled RCTs with standardized vitamin D dosing, OLP severity criteria, validated outcome instruments, and follow-up of at least 12–24 months are needed to definitively establish efficacy, safety, and durability of benefit.
10. **Dose-finding studies:** Dedicated dose-response studies comparing multiple vitamin D supplementation doses (e.g., 1,000, 2,000, 4,000 IU/day) in vitamin D-deficient OLP patients are

needed to define the minimum effective and optimal therapeutic dose.

11. **Patient stratification by VDR genotype:** Pharmacogenomic sub-studies examining VDR gene polymorphisms as predictors of vitamin D treatment response could enable personalized dosing strategies and identify patient subgroups most likely to benefit.
12. **Long-term relapse prevention studies:** Prospective longitudinal studies assessing the impact of sustained vitamin D supplementation on OLP relapse frequency, flare severity, and time to recurrence—particularly in patients with stress-associated exacerbations—would address the clinically critical question of maintenance therapy.
13. **Malignant transformation surveillance studies:** Large prospective cohort studies evaluating malignant transformation incidence in vitamin D-supplemented versus unsupplemented OLP patients, with stratification by OLP subtype, VDR genotype, and supplementation duration, would provide critical data on cancer preventive potential.
14. **Combination micronutrient trials:** Trials examining synergistic combinations of vitamin D with zinc, vitamin B12, or folic acid in OLP management, building on the Aboushousha et al. framework, would provide evidence for comprehensive nutritional supplementation strategies.
15. **Quality of life outcomes:** Future trials should incorporate validated quality of life instruments (e.g., OHIP-14, WHOQOL-BREF) as primary or co-primary outcomes, ensuring patient-centered relevance alongside clinical and biomarker endpoints.
16. **Mechanistic studies in diverse populations:** Expanded molecular mechanistic studies examining VDR expression, cytokine profiling, and Treg/Th17 ratios in OLP patients from diverse geographic and ethnic populations before and after vitamin D supplementation would strengthen mechanistic understanding.

5. CONCLUSION

This comprehensive systematic review provides an integrated synthesis of the evidence linking vitamin D to the pathogenesis and treatment of oral lichen planus. Three convergent lines of evidence—epidemiological, molecular, and clinical—support a biologically plausible and clinically meaningful role for vitamin D in OLP.

From an epidemiological standpoint, OLP patients consistently demonstrate significantly lower serum vitamin D concentrations than healthy controls, with the majority classified as deficient or insufficient, and with lower levels correlating with greater disease severity, particularly in the erosive subtype. From a molecular standpoint, VDR expression is significantly reduced in OLP lesional tissue, and LPS-mediated VDR downregulation in oral keratinocytes creates a pathological cycle whereby mucosal barrier disruption impairs vitamin D signaling, further exacerbating keratinocyte apoptosis and tissue inflammation. Specific VDR gene polymorphisms also confer increased OLP susceptibility, suggesting that genetic variation in vitamin D responsiveness contributes to disease risk.

From a clinical standpoint, adjuvant systemic vitamin D supplementation—particularly in vitamin D-deficient OLP patients—produces statistically significant and clinically meaningful improvements in pain (MD −0.85 to −1.64 across time points) and lesion severity, alongside measurable reductions in IFN-γ and TNF-α—the principal effector cytokines driving OLP pathogenesis. These effects are biologically coherent with calcitriol's well-established immunomodulatory mechanisms, providing mechanistic validation of the clinical observations.

Based on the current evidence, routine assessment of serum 25(OH)D levels in all OLP patients is clinically justified and should be considered standard practice in oral medicine settings. Supplementation to correct documented deficiency or insufficiency is safe, inexpensive, and supported by convergent mechanistic and clinical evidence as an adjuvant to standard OLP therapy, particularly in the erosive and atrophic subtypes. Vitamin D should not replace corticosteroid-based standard therapy but should be considered a rational, low-risk adjuvant in the management algorithm for symptomatic OLP patients with documented deficiency.

However, the existing evidence base remains insufficient to establish definitive clinical guidelines or to specify optimal dosing, duration, or patient selection criteria for vitamin D therapy in OLP. The certainty of the current evidence is constrained by small sample sizes, heterogeneous protocols, short follow-up periods, and predominant focus on vitamin D-deficient populations. The path forward lies in larger, well-designed, multicenter RCTs with standardized protocols, comprehensive biomarker assessment, long-term follow-up, and inclusion of patient-reported quality of life outcomes. Such evidence will determine vitamin D's ultimate position in the OLP treatment algorithm and its potential as a chemopreventive agent against OLP-associated malignant transformation.

In the words of the evolving evidence: vitamin D is not yet a cure for oral lichen planus, but it is an immunologically compelling, clinically promising, and notably well-tolerated addition to the therapeutic armamentarium—one that the oral medicine community has both the scientific rationale and the clinical imperative to investigate further.

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