ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

International Journal of Dental Science and Innovative Research (IJDSIR)

IJDSIR : Dental Publication Service

Available Online at:www.ijdsir.com

Volume – 9, Issue – 3, May – 2026, Page No. : 58 – 66

Neuro-Immune Crosstalk: Redefining Oral Lichen Planus through a Psychoneuroimmunological Lens - A Narrative Review

[1]Dr Prema Priyanka Vallala, BDS, Goregaon Dental Centre, India

Corresponding Author: Dr Prema Priyanka Vallala, BDS, Goregaon Dental Centre, India.

Citation of this Article: Dr Prema Priyanka Vallala, "Neuro-Immune Crosstalk: Redefining Oral Lichen Planus through a Psychoneuroimmunological Lens - A Narrative Review", IJDSIR- May – 2026, Volume – 9, Issue – 3, P. No. 58 – 66.

Type of Publication: Review Article

Conflicts of Interest: Nil

Abstract

Oral Lichen Planus (OLP) is a chronic inflammatory mucosal condition, and current research increasingly explores the psychoneuroimmunological (PNI) pathway as a mechanism through which psychological stress may influence its pathogenesis. This review evaluates the association between psychological stress and OLP, with a particular focus on the role of salivary biomarkers such as cortisol and alpha-amylase in reflecting disease activity. A systematic search of PubMed, Scopus, and Web of Science was conducted, and the synthesis included meta-analyses, observational studies, and clinical trials examining underlying neuroimmune mechanisms. The findings from meta-analytical data demonstrate statistically significant elevations in salivary cortisol levels among OLP patients compared to healthy controls. These results suggest that activation of the hypothalamic–pituitary–adrenal (HPA) axis, along with the subsequent release of pro-inflammatory cytokines such as TNF-α and IL-6, may contribute to immune dysregulation and mucosal damage in OLP. However, variability in outcomes across studies has been noted, which may be attributed to factors such as diurnal variations in biomarker levels and heterogeneity in saliva collection methodologies.

Keywords: Oral Lichen Planus, Psychoneuroimmunology, Psychological Stress, Salivary Biomarkers, Interleukin-6, Salivary Diagnostics, Chronic Inflammation

Introduction

Lichen Planus is an inflammatory, mucocutaneous, antibody and T-cell-mediated autoimmune chronic disorder that affects the mucosa, cutaneous tissue, or both[1,2]. Oral Lichen planus (OLP) can co-exist with genital mucous membrane lesions or with lesions of cutaneous lichen planus[1,2,3]. Within the oral cavity, OLP can occur on any oral mucosa. Still, it is most commonly seen on the buccal mucosa, tongue and gingiva typically manifesting as multiple, bilateral, and symmetrical lesions[2,3]. OLP most commonly affects middle-aged adults, with a higher prevalence in females than males, and is considered a potentially pre-cancerous

condition[2,4,5]. Clinically OLP is broadly classified into Reticular type, characterized by white striae, and erosive type, characterized by painful ulcerations[3]. Although several factors contributing to OLP have been proposed, the exact etiology of the condition remains uncertain[1,4,6]. However, psychological factors such as stress, depression, and anxiety are widely assumed to be major triggering factors for disease onset, flare-ups, and remission[1,6]. This highlights the importance of exploring the association between OLP and psychoneuroimmunology, which examines how psychological stress interacts with the nervous and immune systems.

Saliva serves as a non-invasive diagnostic fluid that can reflect systemic immunological changes. The most significant advantage is that it can be collected easily without inducing any stress in patients. Stress-related biomarkers, including cortisol, alpha-amylase, immunoglobulins, pro-inflammatory cytokines, and oxidative stress markers, have shown potential for assessing disease activity and immune dysregulation in OLP patients [7,8,9]. Studying these markers may offer insight into how stress response pathways contribute to the chronic inflammatory nature of OLP [8,9].

In recent years, increasing attention has been directed toward the role of psychoneuroimmunology in chronic inflammatory diseases, including oral lichen planus. This interdisciplinary field emphasizes the dynamic interaction between psychological processes, neuroendocrine responses, and immune function. Chronic psychological stress has been shown to alter immune homeostasis through sustained activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, leading to changes in cytokine production and inflammatory responses. In the context of oral diseases, such alterations may contribute to the initiation and progression of mucosal lesions. Therefore, understanding these mechanisms is essential for developing a more holistic approach to diagnosis and management, integrating both psychological and biological factors. Despite several individual studies, there remains a need for a comprehensive secondary review that integrates stress, salivary biomarkers, and the neuroimmune mechanisms involved in OLP. Therefore, this review aims to bring together existing evidence on how psychological stress, salivary biomarkers, and neuroimmune pathways interact in oral Lichen Planus.

Objectives

The objective of this review is to synthesize existing literature on the role of psychological stress in the pathogenesis, progression, and exacerbation of oral lichen planus (OLP). It further aims to evaluate the relevance of salivary biomarkers, including cortisol, alpha-amylase, and pro-inflammatory cytokines, in reflecting stress-induced immune dysregulation in affected individuals. Additionally, this review seeks to explore the psychoneuroimmunological (PNI) mechanisms that underpin the interaction between psychological distress and chronic inflammatory responses within the oral mucosa, thereby providing a more integrated understanding of disease dynamics.

Methods / Literature Search Strategy

To review the existing literature, relevant studies were identified through electronic databases including PubMed, Scopus, Web of Science, and Google Scholar. No strict restrictions were placed on the year of publication in order to obtain a comprehensive overview of current knowledge related to psychological stress, salivary biomarkers, and neuroimmune mechanisms in oral lichen planus.

The review focused on evaluating the association between psychological stress and OLP, the role of

salivary biomarkers in assessing disease activity and immune dysregulation, and the neuroimmune pathways linking stress to chronic inflammation. The search terms used included “Oral Lichen Planus,” “psychological stress,” “anxiety,” “depression,” “salivary biomarkers,” “cortisol,” “alpha-amylase,” “cytokines,” “oxidative stress,” and “psychoneuroimmunology.” The literature reviewed included observational studies, clinical studies, case–control studies, and review articles relevant to the objectives of this secondary review.

The Psychoneuroimmunological Mechanism

The findings of this review support the complex interplay between psychological distress and oral pathology. Central to this relationship is the Hypothalamic-Pituitary-Adrenal (HPA) axis[8]. This interaction is a core principle of psychoneuroimmunology, where chronic stress is known to dysregulate immune responses through sustained neuroendocrine activation and altered cytokine signaling[10]. Under chronic stress, the HPA axis is activated, leading to the release of cortisol[8]. While cortisol typically functions as an anti-inflammatory agent, prolonged stress can lead to "glucocorticoid resistance," where immune cells become less sensitive to its effects, thus promoting a pro-inflammatory environment in the oral mucosa (Sancilio et al., 2023). This provides a biological explanation for why anxiety and depression are frequently cited as triggers for OLP flare-ups[5].

Chronic stress also activates the sympathetic-adrenal-medullary (SAM) axis, resulting in increased secretion of catecholamines such as epinephrine and norepinephrine. These neuroendocrine mediators further influence immune cell trafficking, cytokine release, and inflammatory signaling pathways[8]. The combined activation of the HPA and SAM axes creates a sustained pro-inflammatory state, which may contribute to epithelial damage observed in oral lichen planus. Additionally, prolonged exposure to stress hormones may impair regulatory T-cell (Treg) function, thereby reducing immune tolerance and promoting autoimmune responses. This imbalance between pro-inflammatory and anti-inflammatory mechanisms plays a critical role in the persistence and recurrence of OLP lesions[4,8].

Role of Psychological Stress in Oral Lichen Planus

The bidirectional communication between the nervous, endocrine, and immune systems plays a central role in the progression of chronic inflammatory diseases. In OLP, this interaction may lead to persistent immune activation and tissue damage. Understanding this interconnected pathway provides a broader perspective on disease management, emphasizing the importance of both psychological and biological factors[8].

Chronic activation of these interconnected systems may result in sustained immune dysregulation, altered cytokine profiles, and increased susceptibility to inflammatory conditions. In oral lichen planus, this may manifest as persistent mucosal inflammation, delayed healing, and increased frequency of disease exacerbations. These findings further support the role of psychoneuroimmunological mechanisms in linking psychological stress to oral disease progression[8].

The interaction between psychological stress and immune dysregulation in oral lichen planus can be explained through psychoneuroimmunological pathways.

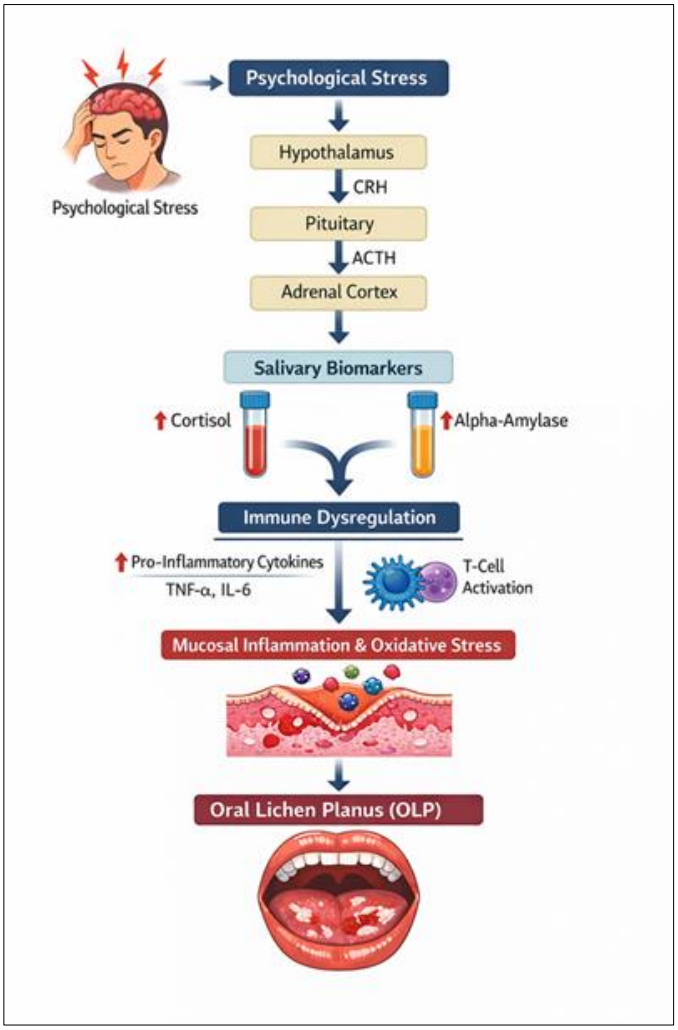

Figure 1:

Figure 1 Proposed psychoneuroimmunological pathway linking psychological stress, salivary biomarkers, and immune dysregulation in Oral Lichen Planus (OLP). Psychological stress activates the hypothalamic-pituitary-adrenal (HPA) axis, resulting in increased cortisol and salivary alpha-amylase[8,6]. These stress-related biomarkers contribute to immune dysregulation, increased pro-inflammatory cytokines (TNF-α, IL-6), and T-cell activation, ultimately leading to mucosal inflammation and the development or exacerbation of OLP[3,4,8].

Synthesis of Biomarker Evidence

The most robust evidence for a biological link comes from meta-analytical data. Lopez-Jornet et al. (2019) performed a comprehensive meta-analysis which demonstrated a statistically significant increase in salivary cortisol levels in OLP patients compared to healthy controls. This confirms that the HPA axis dysregulation is not just a theoretical model but a measurable clinical trend across diverse populations[7,8].

In addition to elevated basal levels, alterations in the diurnal rhythm of cortisol secretion have also been observed in individuals experiencing chronic stress. Normally, cortisol follows a circadian pattern, with peak levels in the morning and a gradual decline throughout the day. However, dysregulation of this rhythm may indicate impaired stress adaptation and has been associated with chronic inflammatory conditions. Such alterations may further contribute to immune imbalance in oral lichen planus, reinforcing the role of cortisol not only as a marker of stress but also as a mediator of disease activity[7,8].

In addition to cortisol and alpha-amylase, other salivary biomarkers such as immunoglobulin A (IgA), oxidative stress markers, and inflammatory mediators have been investigated in OLP patients. These biomarkers provide insight into both local and systemic immune responses and may serve as potential diagnostic and prognostic tools in clinical practice[6,7,9].

In addition to enzymatic and hormonal biomarkers, pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) play a crucial role in the pathogenesis of oral lichen planus. These cytokines are involved in the activation and recruitment of immune cells, particularly cytotoxic CD8+ T-cells, which contribute to epithelial cell damage and chronic inflammation. Elevated levels of these inflammatory mediators have been associated with increased disease severity and may serve as potential indicators of disease activity. The interplay between stress-induced

neuroendocrine responses and cytokine production further highlights the complex immunological environment underlying OLP[4,8]. This is consistent with the established role of CD8+ cytotoxic T-cells in mediating basal keratinocyte apoptosis in OLP lesions[11].

Emerging research has also explored the role of oxidative stress markers in OLP, including reactive oxygen species (ROS) and lipid peroxidation products. Increased oxidative stress may contribute to cellular damage, apoptosis, and further amplification of inflammatory pathways within the oral mucosa[6,9]. Salivary antioxidant capacity has been shown to be reduced in OLP patients, suggesting an imbalance between oxidative and antioxidative mechanisms [6,9]. This imbalance may further interact with stress-induced hormonal changes, creating a complex network of biological interactions that sustain disease progression. Consequently, combining multiple salivary biomarkers rather than relying on a single parameter may provide a more accurate representation of disease activity[7,9]. Several studies have demonstrated significantly elevated levels of lipid peroxidation markers and reduced antioxidant capacity in OLP patients compared to healthy controls[12].

Additionally, the interaction between neuroendocrine mediators and cytokine networks suggests a feedback mechanism in which stress-induced hormonal changes further amplify inflammatory pathways. This bidirectional relationship may lead to a sustained inflammatory state, contributing to chronicity and recurrence of lesions in oral lichen planus. Understanding this complex interaction may provide new insights into targeted therapeutic strategies aimed at modulating both stress responses and immune activity.

Furthermore, variability in salivary biomarker expression may also be influenced by individual factors such as age, gender, circadian rhythm, and psychological status. These variables should be carefully considered when interpreting biomarker levels in clinical and research settings, as they may impact the reliability and reproducibility of findings[6,7].

However, the heterogeneity mentioned in several studies remains a point of discussion. For instance, while the meta-analysis shows a clear trend, individual case-control studies like the one by Skrinjar et al. (2019) have produced null results regarding cortisol levels. These discrepancies are likely due to methodological factors, such as the timing of saliva collection. Glavina et al. (2024) highlighted that salivary biomarkers are subject to significant diurnal variation, suggesting that future research must strictly standardize collection times to ensure accuracy.

Immunological Crosstalk and Future Directions

Beyond cortisol, the role of pro-inflammatory cytokines such as TNF-α and IL-6 cannot be ignored. These cytokines play an important role in the activation and recruitment of cytotoxic CD8+ T-cells that mediate epithelial cell damage in oral lichen planus[4]. Recent Mendelian randomization studies (Chen et al., 2024) suggest a causal link between these inflammatory markers and OLP risk. Furthermore, as we move toward more sensitive diagnostic tools, salivary metabolomics (Kashyap et al., 2024) offers a promising frontier for identifying metabolic "fingerprints" of the disease that go beyond traditional hormone testing.

Clinical Implications

The clinical implications of these findings are significant and extend beyond conventional symptomatic management of oral lichen planus. Incorporating salivary biomarker assessment into routine dental practice may aid in early diagnosis, monitoring of disease activity, and evaluation of treatment outcomes in patients with OLP[7,9]. Furthermore, non-invasive saliva-based diagnostics offer

a patient-friendly approach that can be repeated over time without discomfort. Saliva-based diagnostics have gained increasing recognition as reliable, non-invasive tools for monitoring systemic and oral inflammatory conditions[13].

In addition to biological assessment, integrating psychological evaluation into routine clinical practice may provide a more holistic approach to patient care. Stress management strategies, including cognitive behavioral therapy, relaxation techniques, and lifestyle modifications, may help reduce disease severity and frequency of flare-ups [8]. Collaboration between dental professionals, psychologists, and medical practitioners may therefore be beneficial in managing patients with chronic inflammatory oral conditions.

Moreover, personalized treatment approaches based on biomarker profiling and psychological status may represent a future direction in precision dentistry. Such approaches could improve patient outcomes by targeting both the underlying biological mechanisms and contributing psychosocial factors[8,9]

Emerging Perspectives and Future Directions

Recent advances in research have highlighted the potential role of the oral microbiome in modulating the relationship between psychological stress and oral lichen planus. Emerging evidence suggests that alterations in the oral microbiome may influence immune signalling pathways and contribute to chronic inflammatory conditions such as OLP [14]. Stress-induced alterations in immune function may influence the composition and diversity of oral microbial communities, leading to dysbiosis. This microbial imbalance may further contribute to mucosal inflammation and immune activation, thereby exacerbating disease progression in OLP patients[9]. The interaction between salivary biomarkers, immune mediators, and the oral microbiome suggests a complex, multi-layered network that extends beyond traditional neuroendocrine pathways.

In addition, epigenetic mechanisms are emerging as a potential link between chronic psychological stress and immune dysregulation. Stress-related epigenetic modifications, such as DNA methylation and histone modification, may alter gene expression patterns associated with inflammatory responses and immune regulation. These changes may contribute to long-term susceptibility to inflammatory conditions, including oral lichen planus, even in the absence of ongoing stress exposure[8]. Understanding these molecular-level alterations may provide further insight into the chronic and recurrent nature of the disease. These epigenetic changes have been implicated in long-term immune dysregulation and may contribute to the persistence and recurrence of inflammatory diseases[15].

Furthermore, the integration of advanced diagnostic approaches, including salivary proteomics and metabolomics, offers promising opportunities for early detection and personalized management of OLP. These techniques allow for the identification of specific biomarker profiles associated with disease activity and progression, potentially enabling clinicians to predict flare-ups and tailor treatment strategies accordingly [6,8]. As research continues to evolve, combining molecular diagnostics with psychological assessment may represent a comprehensive approach to improving patient outcomes in oral lichen planus.

Integrated Neuroimmune and Biomarker Dynamics

Beyond individual pathways, the relationship between psychological stress and oral lichen planus should be viewed as a dynamic and interconnected network involving neuroendocrine signalling, immune modulation, and biomarker expression. Chronic activation of the HPA and SAM axes not only alters

cortisol and catecholamine levels but also influences downstream signalling pathways such as nuclear factor-kappa B (NF-κB), which plays a central role in regulating inflammatory gene expression[16,17]. Persistent activation of these pathways may amplify cytokine production, leading to sustained mucosal inflammation and delayed tissue repair.

Additionally, salivary biomarkers may not function as isolated indicators but rather as components of a coordinated biological response reflecting systemic stress adaptation. The combined assessment of cortisol, alpha-amylase, cytokines, and oxidative stress markers may therefore provide a more comprehensive and clinically relevant profile of disease activity. This multi-biomarker approach aligns with emerging trends in precision medicine, where integrated diagnostic models are favored over single-parameter evaluation [18].

Recent evidence also suggests that chronic stress may impair epithelial barrier integrity and alter immune–neural communication, increasing susceptibility to immune-mediated damage in oral tissues [18]. This further supports the concept that psychological stress acts not only as a trigger but also as a perpetuating factor in OLP pathogenesis. Understanding these interconnected mechanisms may facilitate the development of targeted therapeutic strategies aimed at modulating both neuroendocrine and immune pathways.

Limitations of Current Evidence

Despite the insights provided in this review, certain limitations must be acknowledged. Variability in study methodologies, differences in saliva collection protocols, and relatively small sample sizes across studies may affect the consistency of findings. Furthermore, many studies are cross-sectional in nature, limiting the ability to establish a direct causal relationship between psychological stress and oral lichen planus. Additionally, variations in diagnostic criteria and heterogeneity in patient populations across studies may further influence the interpretation of results.

In addition to methodological variability, another important limitation is the lack of standardized protocols for salivary biomarker collection, including differences in timing, stimulation methods, and storage conditions, which may significantly influence biomarker levels and reduce comparability across studies. Furthermore, most available evidence relies on single-time-point measurements rather than longitudinal assessment, limiting the ability to establish temporal relationships between psychological stress and disease progression.

Another critical limitation is the reliance on subjective psychological assessments, such as self-reported stress, anxiety, and depression scales, which may introduce reporting bias and inter-individual variability. Additionally, confounding factors including medication use, systemic conditions, lifestyle habits, and circadian rhythm disturbances are not consistently controlled across studies, potentially affecting the interpretation of results.

Finally, despite emerging evidence on microbiome and epigenetic involvement, these areas remain underexplored in the context of OLP, highlighting the need for integrative, multi-omics approaches in future research.

Conclusion

The integration of psychological and biological data indicates that Oral Lichen Planus (OLP) is not merely a localized mucosal disease, but a condition deeply influenced by systemic psychoneuroimmunological (PNI) factors. The findings of this review confirm that psychological stress acts as a significant catalyst for OLP, mediated by the HPA axis and measurable through salivary cortisol and alpha-amylase.

While certain discrepancies exist in the literature due to methodological variations, the consensus supported by robust meta-analytical evidence points toward a clear association between elevated stress markers and disease activity.

Consequently, incorporating psychological assessments and non-invasive salivary monitoring into clinical practice could significantly improve the management of OLP patients. Future research should prioritize longitudinal studies and standardized collection protocols to fully establish these biomarkers as reliable tools for predicting clinical flare-ups.

A multidisciplinary approach that integrates psychological evaluation, biomarker monitoring, and clinical management may provide a more comprehensive strategy for managing OLP. Future research should focus on longitudinal and large-scale studies to further validate the role of salivary biomarkers in predicting disease progression and therapeutic response.

Acknowledgement

The author sincerely thanks Dr. Anoli Agrawal for her guidance in structuring and organizing the manuscript, as well as for her assistance with formatting and technical aspects of its preparation.

References

1. Manczyk B, Gołda J, Biniak A, Reszelewska K, Mazur B, Zając K, Bińczak P, Chomyszyn-Gajewska M, Oruba Z. Evaluation of depression, anxiety and stress levels in patients with oral lichen planus. Journal of oral science. 2019;61(3):391-7.
2. Cassol-Spanemberg J, Blanco-Carrión A, Rodríguez-de Rivera-Campillo ME, Estrugo-Devesa A, Jané-Salas E, López-López J. Cutaneous, genital and oral lichen planus: A descriptive study of 274 patients. Medicina oral, patologia oral y cirugia bucal. 2018 Dec 24;24(1):e1.
3. Gorouhi F, Davari P, Fazel N. Cutaneous and mucosal lichen planus: a comprehensive review of clinical subtypes, risk factors, diagnosis, and prognosis. The Scientific World Journal. 2014; 2014(1):742826.
4. Chen X, Zhang S, Wu X, Lei Y, Lei B, Zhao Z. Inflammatory cytokines and oral lichen planus: a Mendelian randomization study. Frontiers in Immunology. 2024 Feb 7; 15:1332317.
5. Kashyap B, Hyvärinen E, Laitinen I, Kullaa AM. Salivary metabolomics in patients with oral lichen planus: a preliminary study based on NMR spectroscopy. Clinical Oral Investigations. 2024 Jan 18;28(1):103.
6. Glavina A, Zoranić A, Tadin A, Cigić L, Šupe-Domić D, Lugović-Mihić L. Is salivary A-Amylase a reliable Indicator of psychological status and quality of life in patients with oral lichen planus: a Case-Control study. Cell Physiol Biochemistry: Int J Experimental Cell Physiol Biochem Pharmacol. 2024 Jul 12;58(4):311-21.
7. Lopez-Jornet P, Zavattaro E, Mozaffari HR, Ramezani M, Sadeghi M. Evaluation of the salivary level of cortisol in patients with oral lichen planus: A meta-analysis. Medicina. 2019 May 27;55(5):213.
8. Glavina A, Lugović-Mihić L, Martinović D, Cigić L, Tandara L, Lukenda M, Biočina-Lukenda D, Šupe-Domić D. Association between Salivary Cortisol and α-Amylase with the Psychological Profile of Patients with Oral Lichen Planus and Burning Mouth Syndrome: A Case–Control Study. Biomedicines. 2023 Aug 3;11(8):2182.
9. Carvalho MF, Cavalieri D, Do Nascimento S, Lourenço TG, Ramos DV, Pasqualin DD, Martins LA, Rocha FA, Heller D, Marti L. Cytokines levels and salivary microbiome play a potential role in oral

lichen planus diagnosis. Scientific reports. 2019 Dec 2;9(1):18137.

10. Dantzer R, O'connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nature reviews neuroscience. 2008 Jan;9 (1):46-56.
11. Sugerman PB, Sabage NW. Oral lichen planus: causes, diagnosis and management. Australian dental journal. 2002 Dec;47(4):290-7.
12. Rai B, Kaur J, Jacobs R, Singh J. Possible action mechanism for curcumin in pre-cancerous lesions based on serum and salivary markers of oxidative stress. Journal of oral science. 2010;52(2):251-6.
13. Javaid MA, Ahmed AS, Durand R, Tran SD. Saliva as a diagnostic tool for oral and systemic diseases. Journal of oral biology and craniofacial research. 2016 Jan 1;6(1):67-76.
14. Wang K, Lu W, Tu Q, Ge Y, He J, Zhou Y, Gou Y, Van Nostrand JD, Qin Y, Li J, Zhou J. Preliminary analysis of salivary microbiome and their potential roles in oral lichen planus. Scientific reports. 2016 Mar 10;6(1):22943.
15. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychological bulletin. 2014 May;140(3):774.
16. Black PH. The inflammatory response is an integral part of the stress response: Implications for atherosclerosis, insulin resistance, type II diabetes and metabolic syndrome X. Brain, behavior, and immunity. 2003 Oct 1;17(5):350-64.
17. Tak PP, Firestein GS. NF-κB: a key role in inflammatory diseases. The Journal of clinical investigation. 2001 Jan 1;107(1):7-11.
18. Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. Nature Reviews Immunology. 2011 Sep;11(9):625-32.
19. Skrinjar I, Vidranski V, Brzak BL, Vidovic Juras D, Andabak Rogulj A, Brailo V, Vucicevic Boras V. Salivary cortisol levels in patients with oral lichen planus—A pilot case-control study. Dentistry journal. 2019 Jun 1;7(2):59.