"Pathophysiological Association Between Oxidative Stress and Oral Lichen Planus and its Future Implication on Treatment"

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DOI: https://doi.org/10.51244/IJRSI.2024.11110033

Received: 25 October 2024; Accepted: 03 November 2024; Published: 05 December 2024

ABSTRACT

Objective: This narrative review highlights the relationship between oxidative stress and oral lichen planus, and its implications on the future treatment.

Background data: lichen planus is a chronic, non-contagious, immune-mediated, muco-cutaneous inflammatory disease. The imbalance between antioxidant defense mechanisms and reactive oxygen species homeostasis is one of the numerous reasons proposed by researchers. The dynamic nature of the diseases, with varying clinical forms ranging from moderate to severe forms, as well as anticipated flare-up times and symptom-free intervals that affect patients' quality of life, is what makes them distinctive.

Methodology: Studies with solid evidence served as the foundation for the data collection for this review article. The Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Oral Health Group's Trials Register, EMBASE, PsycINFO, Scopus, and Web of Science were among the thirty databases searched.

Findings: The key players in LP pathogenesis are the inflammatory infiltrate consisting of T cells and the proinflammatory cytokines. The cytokines stimulate the production of reactive oxygen species that induce cell apoptosis, a defining element encountered in LP. The lead inquiry triggered by this revolves around the role of oxidative stress in LP development. The low levels of enzymatic (superoxide dismutase-SOD, catalase-CAT, glutathione peroxidase-GPX) and nonenzymatic antioxidant (vitamin E, A, C, flavonoids, carotenoids, glutathione, plant polyphenols, uric acid, theaflavin, allyl sulfides, curcumin, melatonin, bilirubin, and polyamines) observed in patients with LP suggest a strong relationship with oxidative stress from free radicals, which may significantly contribute to the development of LP lesions.

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue XI November 2024

Conclusion: reactive oxygen species (ROS) overproduction has the potential to initiate autoimmune reactions leading to the development of oral lichen planus (OLP). Identifying new treatment targets and creative target methods requires a thorough understanding of ROS signaling and disease states. Antioxidant therapy is expected to emerge as a novel and promising adjuvant treatment for OLP.

Keywords: Immune mediate inflammatory diseases, Oral lichen planus**,** Oxidative stress, antioxidant, Glutathione peroxide, selenium.

INTRODUCTION

Lichen planus (LP) is a T-cell mediated, chronic mucocutaneous inflammatory condition, in which the oral mucosa is usually involved and can affect approximately 1% of the global adult population with a higher prevalence in middle-aged women. Patients with oral lichen planus may develop extraoral lesions involving the skin, nails, scalp and other mucosal sites such as the genital mucosa [1].

Cutaneous LP is a dermatosis that affects individuals of all ethnicities and sexes equally, with a prevalence that varies from 0.22 to 1%. Planar, purple, polygonal, pruritic, papule and plaque skin lesions are the characteristics that identify the classic condition, according to the so-called "rule six P." White reticulate structures or Wickham's striae on the surface of the lesions are characteristic of LP. Skin alterations restricted to the extremities particularly the wrists, ankles, dorsal surfaces of the hands and feet, and the lumbar region characterize a classic LP. Severe pruritus that is as intense as the affected area but doesn't include obvious scratches or subsequent infections typically follows skin LP. The periods of remission and relapses are the defining characteristics of this disease [2].

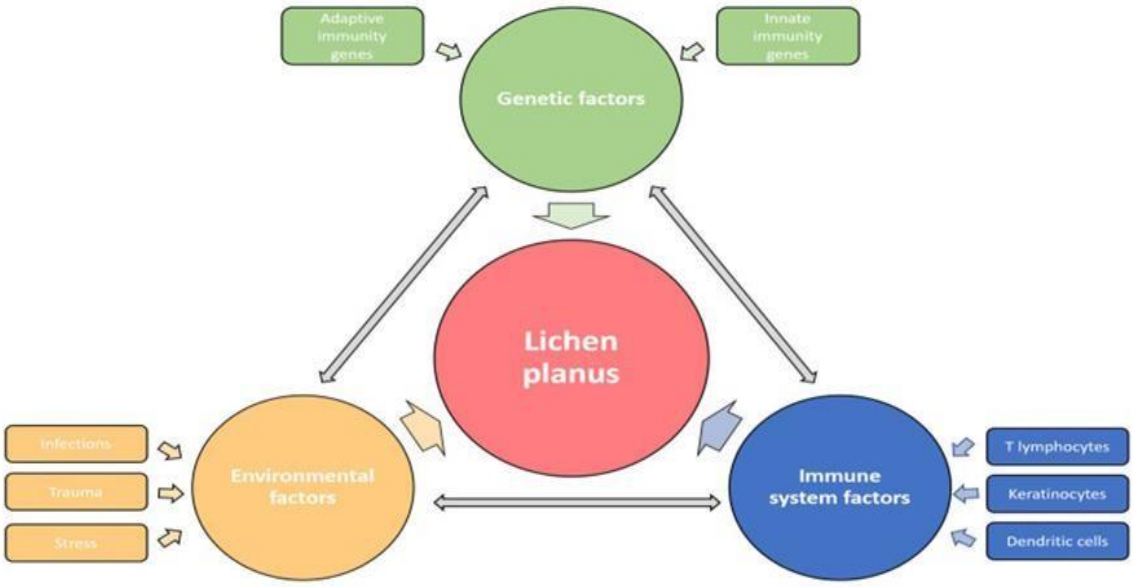
Li et al., 2020 [3]. reported that oral lesions are typically bilateral, frequently symmetric, and most frequently affect the tongue, gingiva, and non-keratinizing buccal mucosa (80%–90% of OLP cases). White or red lesions are the primary clinical characteristic of OLP. Red lesions can cause excruciating agony and discomfort, while the white lesions are typically asymptomatic. OLP can manifest as one of six clinical patterns, either distinct or in combination with reticular, plaque-like, atrophic, erosive/ulcerative, popular, and bullous. Relapses are common in certain patients. As a result, the quality of life is diminished for erosive OLP patients [4].

Etiopathogenesis in OLP:

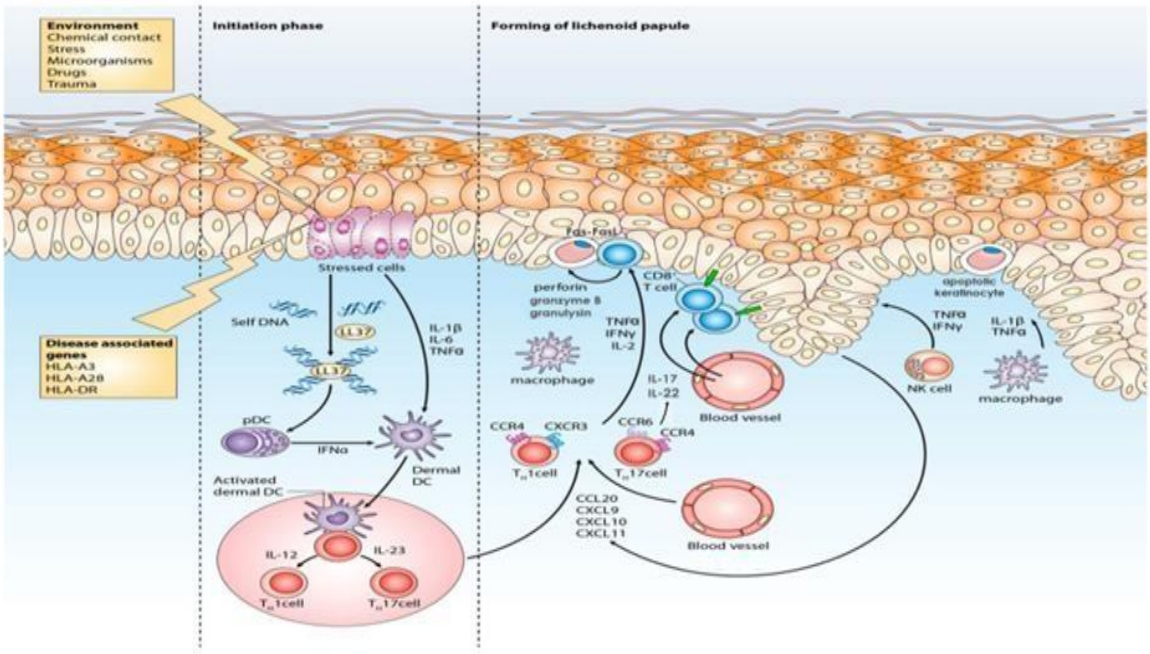
Lichen planus's etiology is not fully understood. It is thought that both internal and external agents are connected to OLP. External factors include the hepatitis C virus, metallic materials, trauma, some medications such as antihypertensives (ß-blockers, thiazides, angiotensin-converting enzyme inhibitors), antirheumatics, antimalarials, gold salts, penicillamine, or retroviral therapies; anti-inflammatory (ibuprofen, diclofenac, naproxen, indomethacin, aspirin, etc.). Majority of the researchers have focused on internal caustic agents such as heat shock protein antigen expression and stress. Infections, diabetes, hypertension, and genetic predisposition are other etiologic factors linked to OLP [5,6].

The immunopathogenesis of LP is triggered by the activation of both the innate and adaptive immune systems, leading to the production of pro-inflammatory cytokines. This include T-cell-mediated immune or autoimmune response to the exogenous or self-altered antigens presented by antigen-presenting cells (APCs) such as keratinocytes. The role of immune dysregulation was mediated by cytotoxic T cells against basal keratinocytes. The initiation phase begins after releasing of damage-associated molecular patterns (DAMPs), which stimulate Toll-like receptors (TLRs). This process triggers the abundant secretion of type I interferon (IFN-α), IL-1β and TNF-α produced by keratinocytes. IFN-α upregulates pro-inflammatory chemokines which then migrate to the regional lymph nodes. There they present the antigens to naïve T lymphocytes and by releasing interleukin (IL) promote the differentiation and expansion of T1 helper and cytotoxic lymphocytes [7,8] fig (1&2)

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue XI November 2024



- Fig(1): Etiological factors involved in the pathogenesis of LP.[8]



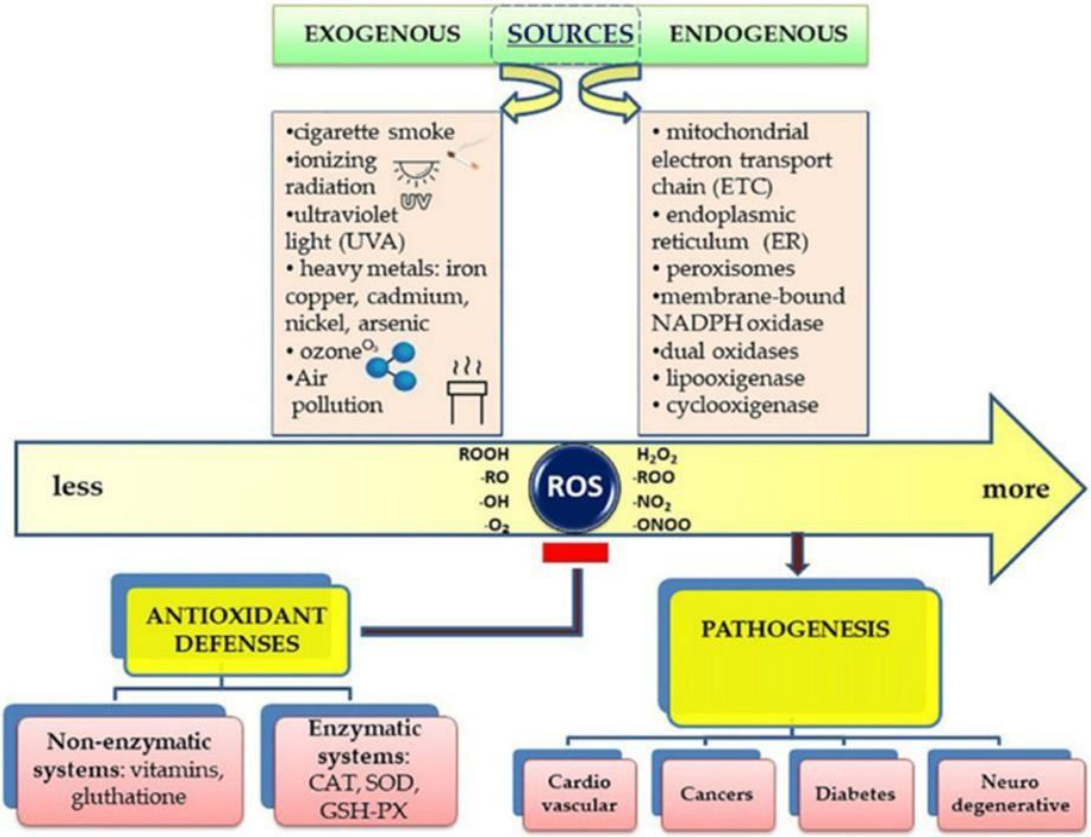
Fig(2): LP immunopathogenesis [8]

The inflammatory process progresses due to reduce the death of inflammatory cells and heightened apoptosis of epithelial cells. The interaction between CD8+ and CD4+ T cells is significant, as it is essential for activating cytotoxicity in affected skin. CD8+ T lymphocytes, upon recognizing antigens presented by keratinocytes through MHC-I molecules, express and secrete mediators that attract more inflammatory cells. Pro-inflammatory cytokines eventually lead to the production of reactive oxygen species (ROS), resulting in cell death [9].

Small, diffusible molecules with one or more unpaired electrons in their outer orbitals are known as the free radicals. These highly reactive substances with single electrons tend to pair up with electrons from other atoms. In chemical terms, oxidation is the loss of one or more electrons. The primary targets of ROS are directed toward mitochondrial DNA, which is crucial for the cell's overall function. While the cell nucleus plays a pivotal role in controlling all cellular functions, the mitochondrion are the key producer of energy, essential metabolites, and cofactors within the cell. Thus, it is clear why communication and coordination between these two central organelles are essential for cell survival [10].

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue XI November 2024

Additionally, mitochondria possess a defense system that enables them to eradicate ROS and repair damage caused by oxidative stress. ROS function as a "double-edged sword" within the human body, serving both beneficial and harmful roles. Under normal physiological conditions, ROS are involved in various signaling pathways, acting as secondary messengers that help defend the body against pathogenic invaders. However, when ROS accumulate and overwhelm the antioxidant defenses, oxidative stress can damage cellular components, including lipids, proteins, carbohydrates, and nucleic acids [11]. Fig (3)



Fig(3) Schematic presentation of the sources of free radicals and their effects on the human body[(10).]

Procedures exist to repair damage, yet some damage is inevitable. Therefore, any changes in the mitochondria must be relayed to the nucleus to modify gene expression, as these changes in DNA structure can have a mutagenic effect that hastens aging and the onset of cancer. The World Health Organization (WHO) currently classifies the disorder as an oral potentially malignant disease because of the risk of malignant transformation, especially in its erosive or ulcerative form, which is considered a high-risk factor (**Giuliani et al. 2019)** [12].

Local aggravating factors such as mechanical irritants, dry mouth, tobacco smoking, and bacterial plaque might affect the illness. Patients should be reassured that OLP is not an infectious disease [13].

Oxidative stress and lichen planus.

Oxidative stress, which is characterized as an imbalance between pro-and anti-oxidant, with a preference for the former, is a major factor in all inflammatory skin disorders. The skin serves as the body's barrier, shielding the body from externals dangers. Because of this, it is constantly exposed to ROS, which cause keratinocyte destruction, and antioxidants. Immune cell recruitment and the release of pro-inflammatory mediators are caused by cell injury. The oxidized molecules generated following tissue injury and increased as a result of inflammation create a harmful cycle that is exacerbated when the body's natural antioxidant system is unable to sufficiently lower OS. The pathogenesis of many diseases is primarily dependent on the disturbance of redox signaling and regulation. ROS mediates the antigen-presenting process that stimulates T-cell activation and controls the interaction between innate and adaptive immune cells [14].

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Many studies have revealed the involvement of oxidative stress in LP pathogenesis. It is also well known that in hepatitis B virus (HCV) infection the balance between oxidants and antioxidants is altered [15,16]. Polyunsaturated fatty acids (PUFAs) are, important components of membrane phospholipids and, major targets of oxidative stress. The skin contains a high amount of PUFAs in the cell membranes and an increased level of iron, both of which amplify the oxidative stress. Oxidative attack against PUFAs leads to the formation of a wide range of metabolites including ethanal, propanal, hexanal, acrolein, glyoxal, malondialdehyde and 4-hydroxynonenal (4-HNE) [17].

Singh et al., 2022 [18]. evaluated salivary oxidative stress in subjects with using monoaldhyde (MDA) and compared it with that in control subjects. Furthermore, to compare MDA levels in erosive and hypertrophic lichen planus were compared. They found that the higher levels of MDA in patients with OLP suggesting that free radicals and the resulting oxidative damage may be important in the pathogenesis of oral lichen planus lesions.

A cross section study done by **Rekha et al 2017 [19].** aimed to evaluate the role of oxidative parameters in the pathogenesis of oral LP by estimating the levels of superoxide dismutase (SOD), malondialdehyde (MDA), glutathione peroxidase (GPx), and uric acid (UA) in saliva of oral LP patients and comparing them with healthy controls. The results showed a significant increase in SOD and MDA in the study group compared to the control group, while GPx decreased. UA value showed an insignificant difference in the same comparison. they concluded that Oxidative stress markers as MDA and SOD are elevated, and GPx is decreased in the saliva of oral LP patients.

Antioxidants systems and lichen planus

Antioxidant systems scavenge free radicals or inhibit the production of reactive oxygen species (ROSs). Conversely, antioxidant mechanisms fix the damage that ROSs have done to different parts of the cell. Antioxidant system often consists of both enzymatic and non-enzymatic substances. Non-enzymatic molecules include albumin, glutathione, melatonin, mycothiol, phenolics, ascorbate, and fibrin which enzymatic components are useful in the antioxidant system and include glutathione peroxidase, glutathione reductase, glutathione-S-transferase, dehydroascorbate reductases, NADPH oxidase, peroxiredoxin, superoxide dismutase, alpha-dioxygenase, ascorbate peroxidase, and catalase [20].

The first line of protection against oxidative stress (OS) occure in the saliva. Saliva contains uric acid, albumin, ascorbate, and enzymes which determine its antioxidant capacity. A class of detoxifying enzymes known as glutathione-S-transferases (GSTs) is present in saliva and is essential for cellular defense against oxidative stress. The human enzyme glutathione reductase (GR), also known as glutathione-disulfide reductase (GSR), is encoded by the GSR gene. Glutathione reductase catalyzes the transformation of glutathione disulfide (GSSG) to glutathione sulfhydryl form (GSH). The levels of glutathione peroxidase were noticeably lower in patients with OLP than in healthy individuals. Analysis of antioxidant components may be a useful way to determine how well the antioxidant system protects cells from oxidative damage [21]

In human cells, glutathione (GSH) is essential for maintaining appropriate functions and preventing oxidative stress in human cells. GSH plays a variety of roles in cell physiology, such as: (i) directly scavenging reactive oxygen species (ROS), nitric oxide (NO), and its derivatives (RNS), protecting DNA, lipids, proteins, and the electron transport chain; (ii) indirectly neutralizing intoxicants; and (iii) controlling the progression of the cell cycle and apoptosis. In addition, it plays a crucial role in metabolism by supporting certain detoxifying enzymes, facilitating transportation, and regenerating antioxidants such as vitamins C and E into reactive forms [22,23,24].

Hassan et al [25].in 2013 evaluated the oxidative stress and the antioxidant defense status in Kashmiri patients with lichen planus. These results indicated an imbalance in the defense mechanisms of LP patients as well as an increase in lipid peroxidation. This could have an impact on the pathophysiology of lichen planus.

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue XI November 2024

Tab[1] Meta-analyses of comparisons of oxidative/antioxidative markers between OLP patients and controls. [14]

Marker (source)	# of studies	OLP, *N*	Control, *N*	Effect size (OLP vs. controls) SMD (95% CI)	*Z* value	*P* value*	Heterogeneity Chi^2	df	*P* value	I^2 (%)
NO (saliva)	4	97	108	3.25 (1.11, 5.39)	2.98	$P = 0.003$	86.4	3	$P < 0.00001$	97
NO (serum/plasma)	2	42	42	1.07 (0.60, 1.53)	4.47	$P < 0.00001$	1.03	1	$P = 0.31$	3
MDA (saliva)	9	307	264	2.38 (1.47, 3.29)	5.13	$P < 0.00001$	138.81	8	$P < 0.00001$	94
MDA (serum/plasma)	4	91	83	0.92 (0.38, 1.46)	3.34	$P = 0.0008$	8.37	3	$P = 0.04$	64
8-OHdG (saliva)	2	70	70	3.78 (0.14, 7.42)	2.04	$P = 0.04$	38.24	1	$P < 0.00001$	97
AOOP (saliva)	2	39	49	1.00 (0.54, 1.45)	4.31	$P < 0.00001$	0.50	1	$P = 0.48$	0
TAC (saliva)	7	267	220	-2.03 (-3.03, -1.03)	3.98	$P < 0.0001$	115.29	6	$P < 0.00001$	95
TAC (serum/plasma)	4	121	109	-2.87 (-4.56, -1.19)	3.34	$P = 0.0008$	57.84	3	$P < 0.00001$	95
Vit C (saliva)	2	76	76	-2.03 (-3.16, -0.89)	3.5	$P = 0.0005$	7.87	1	$P = 0.005$	87
UA (saliva)	5	168	173	-2.65 (-4.20, -1.09)	3.33	$P = 0.00009$	127.97	4	$P < 0.00001$	97
UA (serum/plasma)	3	112	111	-1.19 (-1.83, -0.54)	3.61	$P = 0.0003$	9.77	2	$P = 0.008$	80
Vit A (saliva)	2	98	284	-0.86 (-3.24, 1.52)	0.71	$P = 0.48$	54.52	1	$P < 0.00001$	98
Zn (serum/plasma)	2	101	159	0.21 (-1.73, 2.16)	0.22	$P = 0.83$	47.99	1	$P < 0.00001$	98
GPx (saliva)	3	100	100	-1.34 (-2.81, 0.13)	1.78	$P = 0.07$	42.02	2	$P < 0.00001$	95
Vit E (saliva)	3	138	324	-1.53 (-3.41, 0.34)	1.60	$P = 0.11$	92.75	2	$P < 0.00001$	98
Nitrite (saliva)	2	40	51	-0.23 (-2.81, 2.35)	0.17	$P = 0.86$	30.43	1	$P < 0.00001$	97

TAC = total antioxidant capacity; Vit C = vitamin C; UA = uric acid; NO = nitric oxide; MDA = malondialdehyde; AOOP = advanced oxidation protein product; Vit A = vitamin A; Zn = zinc; GPx = glutathione peroxidase; Vit E = vitamin E.

Treatment of lichen planus:

OLP are frequently treated in a disappointing and contentious manner. Corticosteroids are the most widely recommended medicines for this medical condition because of its ability to reduce the inflammation. Since topical corticosteroids are noninvasive, effective, have few side effects, and are reasonably priced, they are the preferred choice for treating symptomatic OLP. Chronic use of corticosteroid commonly associated with an increased risk for acute pseudomembranous candidiasis. Moreover, there is a considerable chance that systemic absorption from the oral mucosa depresses the adrenal gland [26].

Numerous corticosteroids have been used, each at varying doses and administration schedules. In a study, triamcinolone acetonide was injected locally to 50 erosive OLP patients and low- or medium-dose of prednisolone, a synthetic glucocorticoid was administered orally for 2 weeks to achieve a high and relatively long-lasting local corticosteroid level in a short period of time, and obtained a 90% complete response rate (**Kuo et al.,** 2013) [27]. In another study, the topical 0.1% dexamethasone was administrated for 6 weeks in only 13 patients. The levels of all investigated cytokines, were significantly decreased after the treatment period and the patients' symptoms were decreased in a significant way (**Rhodus et al**., 2006) [28].

Tacrolimus is an immunosuppressive drug and macrolide calcineurin inhibitor, used as an adjunct treatment for OLP. It has been reported to exert a more potent immunological effect while reducing vasoconstrictive and fibrinogenic effects. **Utz et al., 2022** [29]. noted that a 5-year trial demonstrated Tacrolimus's ability to inhibit lesion progression and alleviate subjective complaints. It diminishes the body's immune response by inhibiting the proliferation and normal function of T-lymphocytes. However, despite its efficacy in treating OLP, Tacrolimus is not widely used because of its several side effects, including impaired judgment, post-application burning sensation, nephrotoxicity, hypertension, and its high cost [30,31].

clinical application of antioxidant in treatment of lichen planus:

Suvarna et al [32] conducted a study in order to compare the efficacy of oral zinc 50 mg and 0.1% triamcinolone Orabase with 0.1% triamcinolone Orabase alone on the healing of OLP lesions and concluded that zinc may be a useful adjuvant in the therapy of OLP. Zinc administration relieved the burning sensation and reduced the lesion size.

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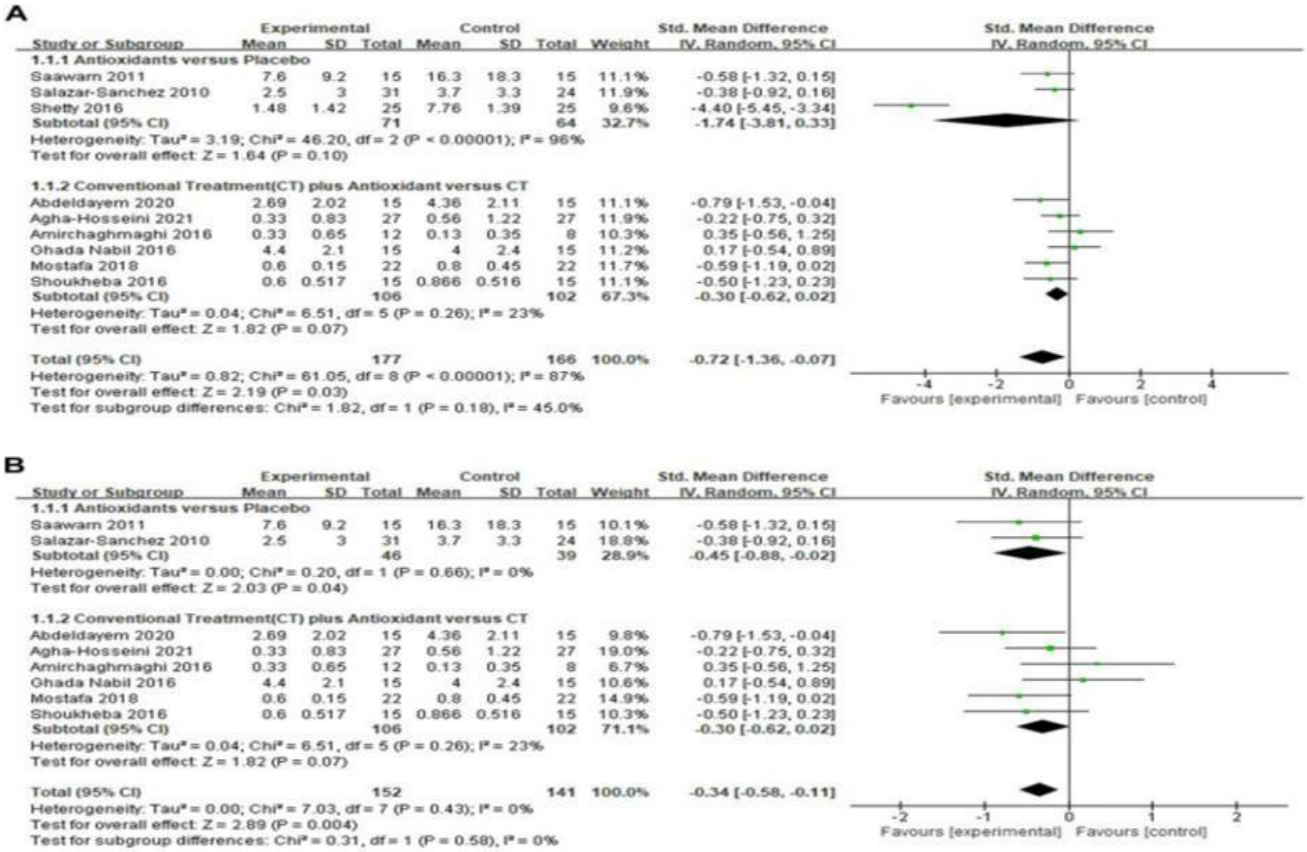
Abdeldayem et al. [33] performed a randomized controlled clinical trial on patients with OLP. They divided the patients into two groups (patients receiving topical triamcinolone acetonide adhesive paste and vitamin E and patients receiving topical triamcinolone acetonide adhesive paste and placebo). The patients receiving vitamin E experienced greater pain reduction and clinical improvement than those receiving placebo. These results show that vitamin E may be useful in the treatment of OLP.

Bedeir et al 2022.[34] evaluated the effectiveness of oral lycopene and systemic steroids in treating erosive oral lichen planus. Twenty patients were divided into two groups: the test group (lycopene) and the control group (corticosteroids). Subjective and objective assessments were conducted at baseline, one, two, and five months after treatment termination. Results showed a significant decrease in objective and subjective outcomes after treatment, with the test group showing better results. However, no significant difference was found between the groups.

Additionally, **Bao et al 2022.[35]** who systematically reviewed the efficacy and safety of antioxidants for Oral lichen planus (OLP) patients. A meta-analysis of 19 studies found that antioxidant therapy significantly reduced pain score and clinical score in OLP patients, improved pain resolution rate, and clinical resolution rate. The study concluded that antioxidant therapy was beneficial for OLP patients and that antioxidants could be used to treat OLP. The meta-analysis included 17 studies with 704 patients and included a risk ratio of 1.15. The findings suggest that antioxidants may be a potential treatment option for OLP.

Tab [2] Antioxidant therapy for patients with oral lichen planus: A systematic review and meta-analysis[35]



DISCUSSION

Oral Lichen Planus (OLP) biomarkers, are increasingly focusing on identifying the disease indicators in non-invasively collected materials like saliva. This trend stems from the ease of collecting saliva and its potential as a non-invasive substitute for tissue biopsies. Saliva collection is simple and can be done repeatedly, circumventing the discomfort associated with invasive methods such as blood or tissue sampling. The study aims to evaluate the levels of certain antioxidants, namely the enzymatic antioxidant glutathione peroxidase (GPx) and the non-enzymatic antioxidant uric acid (UA), in the saliva of OLP patients.

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Aly and Shahin 2010 [15]. who evaluated 45 Egyptian LP patients and 45 healthy volunteers as age- and sex-matched the control patients. Serum levels of nitric oxide (NO), malondialdehyde (MDA), superoxide dismutase (SOD), and erythrocyte catalase (CAT) levels were measured. They reported that the pathophysiology of LP is influenced by elevated oxidative stress and an imbalance in the antioxidant defense mechanisms.

The deeper the understanding of the pathogenesis of OLP disease has led to the development of a novel therapeutic options that target key molecules in the immune system or the pathological pathways. The success of these new therapies lies in their high selectivity of action, which in most cases provides significant therapeutic efficacy in a short time with fewer side effects compared to traditional therapies. The antioxidants potential in this phase of therapeutic revolution and, studies on drugs that target OS have become increasingly frequent. Antioxidants are substances that neutralize ROS and, preventing cell and tissue damage. Antioxidant Therapy may act as a safe alternative therapy to the long-term use of nonsteroidal anti-inflammatory drugs, patients who are resistant to the standard treatment protocols or treatment by other drugs that are associated with adverse effects [36]. The antioxidants studied were included vitamin E, purslane, hyaluronic acid, curcumin, curcuminoids, aloe vera, green tea, ozone, lycopene, cedar honey, and coenzyme Q10.

A meta-analysis by **Bao et al 2022 [35],** reviewed the efficacy and safety of antioxidants for patients with Oral lichen planus (OLP). They demonstrated that antioxidant therapy was beneficial for patients with OLP, and the antioxidants could be used to treat OLP.

A randomized controlled clinical trial by **Abdeldayem et al** [33]**,** assessed the effect of systemic use of vitamin E in symptomatic patients with OLP. They divided the patients into two groups (patients receiving topical triamcinolone acetonide adhesive paste and vitamin E and patients receiving topical triamcinolone acetonide adhesive paste and placebo). The patients receiving vitamin E experienced greater pain reduction and clinical improvement than those receiving placebo. These results show that vitamin E may be useful in the treatment of OLP. **Suvarna et al**. [32] conducted a study in order to compare the efficacy of oral zinc 50 mg and 0.1% triamcinolone Orabase with 0.1% triamcinolone Orabase alone on the healing of OLP lesions and concluded that zinc may be a useful adjuvant in the therapy of OLP. Zinc administration relieved the burning sensation and reduced the lesion size. The adjunctive use of systemic vitamin E and Zinc showed a promising outcomes in the management of OLP with no side effects.

Selenium is an essential trace element with antioxidant effects and is found naturally in the human body. It acts against oxidative stress, slows down the aging process, and inhibits viral infections while playing an important role in chemoprevention, metabolism and immune system modulation. Selenium efficacy mediated by glutathione peroxidases (GPx) 4 which remove the potentially damaging hydrogen peroxide [37,38].

A 2011 study by **Barikbin et al** [39], on 30 patients with LP revealed a significant positive correlation between selenium and GPx levels in the serum of both patients. Glutathione sulfhydryl (GSH) levels were significantly lowered in LP patients compared to controls. This may be due to the augmented GSH turnover rate as a defense mechanism against oxidative stress. Thus, selenium may be a promising immune-modulator, with antioxidant and anti-inflammatory properties.

CONCLUSION

The oral manifestations of Lichen planus diseases often precede the systemic symptoms. Dentist can be the cornerstone in the early diagnosis of LP. Understanding the clinical symptoms and diagnosis of this disease are important for the accurate treatment of these lesions. Glutathione reductase levels may be used as a biomarker of OLP for monitoring and treatment. Antioxidant medication may act as a promising immunomodulator with anti-inflammatory efficacy for the treatment of OLP.

Funding: no external funding.

Ethical approval: No ethical concern

Data Availability: Public available.

Conflicts of Interest: The authors declare no conflict of interest

The paper is published as a preprint. It has been assigned a DOI and is now a permanent and citable part of the scholarly record. The DOI is: 10.17632/6g6gnc7x2v.1

The URL is: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4872952.

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