# Oxidative Stress and Its Markers in Pathogenesis and Diagnosis of Oral Potentially Malignant Disorders

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***Abstract*—Background: Oral potentially malignant disorders (OPMDs) — including oral leukoplakia, oral submucous fibrosis (OSMF), and oral lichen planus (OLP) — are chronic mucosal lesions carrying substantial risk of progression to oral squamous cell carcinoma (OSCC).[1,2] Oxidative stress, arising when reactive oxygen species (ROS) exceed antioxidant defence capacity, plays a pivotal role in OPMD initiation and progression by inducing lipid peroxidation, DNA injury, and protein modification.[3,4]**

**Objectives: To summarise current evidence on oxidative stress mechanisms, key markers, and their clinical utility in the diagnosis and prognosis of OPMDs.**

**Methods: A narrative review of peer-reviewed literature was conducted. Thirty high-quality references spanning systematic reviews, cohort studies, and experimental investigations were included.**

**Results: Patients with OPMDs consistently demonstrate elevated malondialdehyde (MDA), nitric oxide (NO), and 8-hydroxy-2-deoxyguanosine (8-OHdG), alongside reduced superoxide dismutase (SOD), catalase, glutathione, and total antioxidant capacity (TAC).[5,6] These changes correlate with degree of dysplasia and malignant transformation risk.[7,8]**

**Conclusion: Oxidative stress markers — measurable non-invasively in saliva — are valuable adjunct tools for early detection, risk stratification, and monitoring of OPMDs. Integration of antioxidant biomarker assessment into clinical practice may improve patient outcomes.**

***Index Terms*—Oral potentially malignant disorders; oxidative stress; malondialdehyde; reactive oxygen species; antioxidants; saliva; oral leukoplakia; oral submucous fibrosis; oral lichen planus**

## I. INTRODUCTION

Oral potentially malignant disorders (OPMDs) affect millions globally and represent a clinically significant spectrum of mucosal changes that precede oral squamous cell carcinoma (OSCC).[1] The World Health Organization recognises OPMDs as lesions with a higher risk of malignant transformation than normal tissue;[2] common entities include oral leukoplakia, OSMF, OLP, erythroplakia, and actinic cheilitis.[3,4] These conditions share key features: persistent epithelial dysplasia, chronic inflammation, and varying degrees of architectural disturbance.[5,6]

The aetiology is multifactorial, involving tobacco, areca nut, alcohol, nutritional deficiency, and immune dysregulation.[7] Among the molecular mechanisms implicated, oxidative stress has emerged as a central driver. ROS — including superoxide radicals, hydroxyl radicals, and hydrogen peroxide — are produced during normal metabolism; when their generation exceeds the neutralising capacity of enzymatic and non-enzymatic antioxidants, cellular damage ensues.[8,9] This damage encompasses lipid peroxidation of cell membranes, strand breaks and base modifications in DNA, and protein carbonylation, all of which can promote dysplasia and carcinogenesis.[10,11]

Clinical interest has focused on quantifying oxidative stress markers in accessible biological fluids. Saliva, in direct contact with oral lesions, is particularly attractive because it is collected non-invasively and reflects both local mucosal and systemic oxidative changes.[12,13] Elevated markers such as MDA and 8-OHdG, combined with reduced SOD and TAC, have been documented across multiple OPMD subtypes and correlate with lesion severity.[14,15] This review consolidates current evidence on the pathogenic role of oxidative stress and the diagnostic and prognostic utility of its markers in OPMDs.[16,17]

## II. ORAL POTENTIALLY MALIGNANT DISORDERS

### 2.1 Definition and Classification

The WHO defines OPMDs as mucosal lesions with a statistically greater likelihood of malignant conversion than surrounding normal tissue.[1,2] The preferred terminology acknowledges that transformation is not inevitable, but histological dysplasia, particularly moderate-to-severe grades, significantly elevates individual risk.[3] Oral leukoplakia is the most prevalent OPMD, presenting as white patches that cannot be rubbed off and cannot be characterised clinically or pathologically as any other condition; erythroplakia carries the highest dysplastic potential with up to 50% of lesions harbouring carcinoma in situ at biopsy; OSMF is strongly linked to areca nut use and is characterised by progressive submucosal fibrosis causing trismus; OLP is immune-mediated and its malignant potential, particularly in the erosive/atrophic forms, remains an area of ongoing debate; and actinic cheilitis arises from cumulative ultraviolet exposure of the lower lip.[4,5,6] Collectively, OPMDs impose a substantial public health burden, particularly in South and Southeast Asia where tobacco and areca nut habits are widespread. Estimated global prevalence of leukoplakia is 1–5%, while OSMF affects hundreds of millions of areca nut users.[18,19,20,21.]

### 2.2 Malignant Transformation Risk

The annual malignant transformation rate of oral leukoplakia ranges from 0.13% to 17.5% depending on clinical subtype, location, and degree of dysplasia.[1,7] Non-homogeneous leukoplakia, lesions on the floor of mouth or lateral tongue, presence of Candida infection, and female sex in non-smokers are recognised as higher-risk features.[4,7] Erythroplakia and erythro-leukoplakia carry transformation rates as high as 30–40%.[16] OSMF has an estimated transformation rate of 7–13%, closely associated with areca nut habit duration and intensity.[10,22] The capacity to predict which individual lesions will transform remains limited by reliance solely on clinical and histopathological parameters, underscoring the need for reliable molecular biomarkers — including oxidative stress markers — to augment risk stratification.[8,17]

## III. OXIDATIVE STRESS: MECHANISMS AND SOURCES

### 3.1 Definition and Molecular Basis

Oxidative stress is defined as a sustained imbalance between ROS generation and antioxidant defence, resulting in net oxidative damage to biomolecules.[9,23] Under normal physiological conditions, small quantities of free radicals (molecules with unpaired electrons )are generated as metabolic by-products and are rapidly neutralised by cellular antioxidant systems. When this balance is disrupted, free radical concentrations rise to levels that damage lipids, proteins, and nucleic acids.[24,25] Three primary categories of reactive species are recognised: reactive oxygen species (ROS), including superoxide anion ($O_2^-$), hydrogen peroxide ($H_2O_2$), and the highly reactive hydroxyl radical (•OH); reactive nitrogen species (RNS), principally nitric oxide (NO•) and peroxynitrite ($ONOO^-$); and secondary lipid-derived radicals produced during peroxidation chain reactions.[23,24] In the context of OPMDs, chronic and repeated exposure to carcinogenic stimuli such as tobacco smoke, areca nut alkaloids, alcohol, and inflammatory mediators ,sustains ROS/RNS generation at levels that overwhelm compensatory responses, creating a pro-carcinogenic cellular environment.[18,25,26]

### 3.2 Sources of ROS in OPMDs

Endogenous ROS arise from mitochondrial electron transport chain leakage (accounting for up to 5% of consumed oxygen under normal conditions), xanthine oxidase activity, cytochrome P450 metabolism, NADPH oxidase activity in phagocytes, and peroxisomal oxidation.[23,25] In OPMD tissues,

infiltrating neutrophils and macrophages generate a significant oxidative burst during immune activation, substantially amplifying ROS load.[14,27] Exogenous sources include tobacco combustion products (including benzo[a]pyrene quinones and acrolein), areca nut-derived reactive compounds (arecoline, arecaidine), alcohol metabolite acetaldehyde, ionising radiation, heavy metals, and environmental pollutants.[18,22,26] These exogenous agents not only directly generate ROS but also impair antioxidant enzyme function, compounding the oxidative burden sustained by oral epithelial cells.[9,25]

### 3.3 Reactive Nitrogen Species

Reactive nitrogen species — principally nitric oxide produced by inducible nitric oxide synthase (iNOS) during chronic inflammation — contribute significantly to tissue damage in OPMDs.[15,27] NO itself reacts with superoxide to form peroxynitrite, a potent oxidant capable of nitrating tyrosine residues in proteins (forming nitro tyrosine), inducing single-strand DNA breaks, and oxidising guanine to 8-nitroguanine.[15,27] Elevated salivary and tissue NO levels have been documented in OLP and OSMF patients, reflecting the sustained inflammatory state characteristic of these lesions.[15,27] RNS-mediated protein modification disrupts enzyme function, receptor signalling, and cell adhesion molecules, potentially facilitating epithelial-to-mesenchymal transition — an early step in malignant progression.[23,24]

## IV. ANTIOXIDANT DEFENCE SYSTEM IN OPMDS

### 4.1 Enzymatic Antioxidants

The enzymatic arm of antioxidant defence constitutes the first line of protection against ROS accumulation such as superoxide dismutase and glutathione peroxide.[9,12,23,24] Superoxide dismutase (SOD) catalyses the dismutation of superoxide anion to hydrogen peroxide and molecular oxygen. Three mammalian SOD isoforms exist: cytosolic Cu/ZnSOD (SOD1), mitochondrial MtSOD (SOD2), and extracellular SOD (SOD3). Hydrogen peroxide generated by SOD is subsequently detoxified by catalase (primarily in peroxisomes) or glutathione peroxidase (GPx) in the cytosol and mitochondria.[9,12] Catalase converts $H_2O_2$ to water and oxygen, preventing its reduction to the highly toxic hydroxyl radical via Fenton chemistry. Glutathione peroxidase utilises reduced glutathione (GSH) as a co-substrate to neutralise both $H_2O_2$ and organic lipid peroxides, oxidising GSH to GSSG. Glutathione reductase then regenerates GSH from GSSG using NADPH.[9,12,23] Additional protective enzymes include paraoxonase-1 (PON1), which protects against lipid oxidation, thioredoxin reductase, and peroxiredoxins.[24]Reduced activity of these enzymatic antioxidants — including SOD, catalase, GPx, GSH, and NADPH — has been consistently documented in leukoplakia and oral submucous fibrosis (OSMF), with the degree of depletion correlating with lesion severity and dysplasia grade.

### 4.2 Non-Enzymatic Antioxidants

Non-enzymatic antioxidants contribute substantially to total antioxidant capacity (TAC) in saliva and plasma.[23,24] Vitamin C (ascorbic acid) is a water-soluble free radical scavenger and also regenerates vitamin E after oxidation. Vitamin E (α-tocopherol) is a lipid-soluble antioxidant that terminates lipid peroxidation chain reactions within cell membranes.[23] Uric acid is the principal contributor to salivary TAC and a potent scavenger of peroxynitrite and hydroxyl radicals. Glutathione, in addition to its enzymatic role, directly scavenges hydroxyl radicals and singlet oxygen. β-Carotene, lycopene, and bilirubin contribute additional free-radical scavenging capacity.[24.] Depletion of these non-enzymatic antioxidants has been reported in leukoplakia, OSMF, and oral lichen planus, supporting their role as biomarkers of oxidative stress in OPMDs. OPMD tissues, chronic oxidant exposure progressively depletes both enzymatic and non-enzymatic antioxidant reserves. Reduced SOD, catalase, GPx, and GSH have been consistently documented across leukoplakia, OSMF, and OLP, with the magnitude of depletion broadly correlating with disease severity and dysplasia grade.[9,12,23,24] Paradoxically, some studies report an initial SOD elevation as a transient compensatory response before ultimate depletion in advanced lesions, a finding that underscores the dynamic nature of the antioxidant response to evolving oxidative load.[9] Total antioxidant capacity, measured by FRAP, DPPH, or ORAC assays, is consistently reduced in saliva and serum of OPMD patients compared with healthy controls, and lower

TAC values have been associated with higher dysplasia grades and greater risk of malignant transformation.[9,12,23,24]

## V. ROLE OF OXIDATIVE STRESS IN OPMD PATHOGENESIS

### 5.1 Lipid Peroxidation and Membrane Damage

Lipid peroxidation is an early and prominent consequence of oxidative stress in which ROS attack polyunsaturated fatty acids (PUFAs) in cell membranes, initiating self-propagating chain reactions that generate cytotoxic aldehydes.[9,12] Malondialdehyde (MDA) is the most widely studied end-product; it disrupts membrane fluidity and integrity, impairs membrane-bound receptor and ion channel function, forms mutagenic MDA-DNA adducts (notably M1dG), and can cross-link proteins.[23,24] 4-Hydroxynonenal (4-HNE), another major lipid peroxidation product, reacts with lysine, histidine, and cysteine residues in proteins, impairing their function and activating stress-signalling pathways such as NF-κB and MAPK that promote survival of damaged cells.[23] Elevated MDA has been consistently reported in saliva and serum of OPMD patients , including oral leukoplakia, OSMF, and OLP compared with healthy controls, with highest levels in dysplastic and advanced lesions.[9,12,23,24]

### 5.2 DNA Damage and Genetic Instability

ROS cause a spectrum of DNA lesions, including single- and double-strand breaks, oxidative base modifications, a basic sites, and DNA-protein cross-links.[25,26] Among oxidative base modifications, 8-hydroxy-2-deoxyguanosine (8-OHdG) — formed by hydroxyl radical attack on the C-8 position of guanine — is the most extensively studied biomarker of oxidative DNA damage. 8-OHdG is a pre-mutagenic lesion: if not repaired before DNA replication, it pairs with adenine rather than cytosine, generating G→T transversion mutations ( a mutational signature )commonly observed in *TP53* and *KRAS* in oral cancer.[23,24] Elevated 8-OHdG levels in OPMD tissues , particularly in tobacco and areca nut users — have been documented as early indicators of genotoxic stress that precede frank dysplasia, making 8-OHdG a promising predictive biomarker.[8] Chromosomal instability resulting from persistent double-strand breaks further contributes to genomic instability, allelic loss at tumour suppressor loci, and clonal evolution of dysplastic cells.[25,26]

### 5.3 Protein Oxidation

Oxidative stress induces direct modification of cellular proteins through carbonylation (oxidation of proline, arginine, lysine, and threonine residues), formation of disulphide cross-links, and methionine sulphoxidation.[23,24] Protein carbonylation, measured as advanced oxidation protein products (AOPP) or directly by DNPH assay, is a sensitive indicator of chronic oxidative injury. Oxidised proteins lose catalytic activity, structural integrity, and regulatory function; they also accumulate because oxidised proteins are less efficiently degraded by the proteasome.[24] The resultant disruption of cellular metabolism, including impaired DNA repair enzyme activity, further increases mutation rates in OPMD epithelium.[23]

### 5.4 Inflammation, Fibrosis, and Cell Signalling

Chronic inflammation amplifies oxidative damage through continuous ROS/RNS release from neutrophils and macrophages, establishing a self-perpetuating cycle of tissue injury.[14,27] In OSMF, areca nut alkaloids (principally arecoline) directly stimulate fibroblasts to produce excess collagen while simultaneously generating ROS that activate TGF-β1 signalling, further promoting fibroblast activation and collagen cross-linking. This results in progressive submucosal fibrosis, reduced vascularity, epithelial atrophy, and antioxidant depletion.[10,11,12,22] In OLP, persistent T-cell-mediated basal cell destruction generates RNS that modify epithelial proteins, activate NF-κB, and promote a pro-inflammatory cytokine milieu (TNF-α, IL-6, IL-17).[15,27] Excess ROS and RNS can activate EGFR, Ras/MAPK, PI3K/Akt, and NF-κB pathways, promoting cell survival, proliferation, and evasion of apoptosis.[23,24] Progressive accumulation of these molecular lesions disrupted DNA repair, mutated tumour suppressors, aberrant survival signalling, and impaired apoptosis collectively create conditions permissive for clonal expansion and malignant transformation.[7,16,17]

## VI. KEY OXIDATIVE STRESS MARKERS IN OPMDS

| Marker | Mechanism | Clinical Significance in OPMDs |
|---|---|---|
| Malondialdehyde (MDA) | Primary lipid peroxidation end-product; forms DNA adducts and disrupts membrane function. | Elevated in leukoplakia, OSMF, OLP; highest in severe dysplasia. Correlates with lesion severity. |
| 8-OHdG | Oxidative guanine base modification; marker of genotoxic stress and DNA repair failure. | Elevated in OPMD tissues and saliva; predictor of malignant transformation risk. |
| Nitric oxide (NO) | RNS produced during inflammation; excess NO generates peroxynitrite, damaging proteins and DNA. | Elevated in OLP, OSMF; reflects inflammatory burden and nitrosative stress. |
| Superoxide dismutase (SOD) | Converts superoxide to $H_2O_2$; first-line antioxidant enzyme defence. | Reduced in OPMDs (depleted antioxidant system); occasional early increase as compensatory response. |
| Catalase | Decomposes $H_2O_2$ to water and $O_2$; prevents hydroxyl radical formation. | Reduced activity in OPMDs; correlates with oxidative epithelial damage. |
| Glutathione (GSH) | Major intracellular thiol antioxidant; substrate for GPx; scavenges multiple ROS species. | Consistently decreased in OPMDs; magnitude of depletion linked to dysplasia grade. |
| Total antioxidant capacity (TAC) | Composite measure of all antioxidant defences in a biological sample. | Reduced in leukoplakia, OSMF, OLP; inversely associated with oxidative damage severity. |
| TBARS / Lipid perox. products | Thio barbituric acid reactive substances; indirect but widely used measure of MDA. | Elevated in serum and saliva; useful for large-scale screening studies. |

Table 1. Principal oxidative stress markers, their mechanisms, and clinical significance in OPMDs. OSMF = oral submucous fibrosis; OLP = oral lichen planus.

## VII. SALIVARY AND SERUM DIAGNOSTIC APPLICATIONS

### 7.1 Saliva as a Diagnostic Fluid

Saliva has gained prominence as a diagnostic medium for OPMDs because it is in direct contact with oral lesions, can be collected non-invasively by passive drool or unstimulated spitting into sterile containers, and reflects both local mucosal biochemistry and systemic oxidative status.[12,13,19] Compared with blood-based investigations, salivary analysis eliminates needle-related discomfort, does not require trained phlebotomists, is suitable for paediatric and needle-phobic patients, and allows repeated sampling for longitudinal monitoring without patient burden.[9,12] Saliva contains a rich array of oxidative stress markers — MDA, NO, 8-OHdG, $H_2O_2$, protein carbonyls — alongside antioxidants including SOD, catalase, GPx, GSH, TAC, uric acid, and vitamin C.[23,24] Because lesional epithelium is directly bathed in saliva, local oxidative changes may be detectable in salivary analysis before systemic markers become abnormal, potentially offering an earlier diagnostic window.[9,12,19]

### 7.2 Key Salivary Findings Across OPMD Subtypes

Studies consistently report elevated salivary MDA, NO, and 8-OHdG alongside reduced SOD, catalase, GSH, and TAC in leukoplakia, OSMF, and OLP patients compared with healthy controls.[9,12,15,23,24] In oral leukoplakia, salivary MDA has been shown to increase proportionally with dysplasia grade, and salivary SOD and catalase are inversely reduced.[7,9] In OSMF, elevated salivary lipid peroxidation products and reduced GSH correlate with clinical stage and degree of fibrosis, reflecting the progressive oxidative burden imposed by ongoing areca nut exposure.[12,22] In OLP, elevated salivary NO and MDA reflect the ongoing inflammatory oxidative injury, and their levels are reported to be higher in erosive/atrophic forms i.e.,the subtypes with greater malignant potential — than in reticular OLP.[15,27] Significant correlations between salivary and serum marker levels have been demonstrated across multiple studies, supporting saliva as a clinically viable alternative to blood-based testing.[9,12,19]

7.3 Clinical Diagnostic Utility

The diagnostic and prognostic utility of salivary oxidative markers encompasses four key domains.[8,23,24] First, for early detection, biochemical changes precede clinically visible progression, enabling identification of high-risk individuals before severe dysplasia develops; elevated MDA and reduced TAC have been detected even in mild, clinically non-dysplastic leukoplakia.[9,12,19] Second, for risk stratification, higher oxidative damage and lower antioxidant levels distinguish patients likely to progress from those with stable lesions; patients with long-standing tobacco and areca nut habits demonstrate the greatest oxidative imbalance and correspondingly higher transformation risk.[7,9,12,28] Third, for disease monitoring, serial salivary measurements allow non-invasive tracking of treatment response or the effects of habit cessation; improvement in MDA and TAC levels following antioxidant therapy or tobacco cessation provides objective biochemical evidence of clinical benefit.[9,12,19] Fourth, for malignant transformation prediction, lesions with persistently elevated MDA, 8-OHdG, and reduced GSH are significantly more likely to progress to OSCC, and these markers may complement , though not replace ,histopathological biopsy in clinical decision-making.[8,9,23,24]

## VIII. PROGNOSTIC SIGNIFICANCE

8.1 Correlation with Lesion Severity and Dysplasia Grade

Cumulative evidence indicates that the degree of oxidative imbalance is proportional to clinical and histopathological severity in OPMDs.[9,12,19] Lesions with mild epithelial changes show moderate elevations in oxidative markers, whereas moderate-to-severe dysplasia is associated with significantly higher MDA and 8-OHdG and more pronounced antioxidant depletion.[7,8,9,23,24] In leukoplakia, salivary MDA and 8-OHdG levels in patients with moderate-to-severe dysplasia are significantly higher than in patients with mild or no dysplasia, and SOD and catalase show reciprocal reductions.[7,9] This dose-response relationship between oxidative marker magnitude and dysplasia grade supports their use in grading oxidative risk and prioritising patients for more frequent biopsy surveillance.[8,23]

8.2 Prediction of Malignant Transformation to OSCC

Comparative studies between OPMD and OSCC patients demonstrate that oxidative damage markers — MDA, 8-OHdG, NO, protein carbonyls — are substantially higher in malignant tissue than in precancerous lesions, and that reduced protective antioxidants (GSH, SOD, catalase) further increase cellular susceptibility to cancerous transformation.[8,9,23,24,28] Studies that have followed OPMD patients longitudinally indicate that those who ultimately developed OSCC had significantly higher baseline oxidative marker levels and lower antioxidant capacity at initial evaluation than those whose lesions remained stable or regressed.[8,28] Markers such as MDA, 8-OHdG, and the GSH/GSSG ratio have been proposed as part of multi-marker predictive panels to identify high-transformation-risk lesions.[23,24] Collectively, these findings establish oxidative stress profiling as a meaningful complement to histopathological grading, particularly for identifying which OPMD patients warrant closer surveillance, chemoprevention, or earlier surgical intervention.[19,23,28]

## IX. DISCUSSION

The collective findings reviewed here establish a robust mechanistic and clinical framework

connecting oxidative stress to the pathogenesis and clinical behaviour of OPMDs.[9,12,23,24] Several themes merit emphasis. First, the oxidative changes observed in OPMDs are not merely epiphenomena of tissue damage , they are active drivers of carcinogenesis. ROS-mediated DNA mutations, lipid peroxidation products that form mutagenic adducts, and RNS-induced protein modifications collectively create a molecular milieu conducive to genomic instability, dysregulated proliferation, and impaired apoptosis.[23,24,25] Second, the gradient of oxidative damage , increasing from normal mucosa through mild and moderate dysplasia to severe dysplasia and carcinoma further supports oxidative stress assessment as a dynamic and biologically meaningful measure of disease stage.[7,8,9]

An important clinical consideration is the differential contribution of specific OPMD subtypes to overall oxidative burden. In OSMF, the areca nut alkaloid arecoline directly stimulates ROS generation and fibroblast activation via TGF-β1, and oxidative stress compounds the epithelial atrophy associated with progressive fibrosis, explaining the particularly high malignant transformation rate seen in advanced OSMF.[10,11,12,22] In OLP, immune-mediated tissue destruction and RNS production from activated T-cells and macrophages constitute the primary oxidative mechanism, with the erosive/atrophic subtypes demonstrating greater oxidative burden and correspondingly higher malignant risk than reticular forms.[14,15,27] In leukoplakia, non-homogeneous subtypes and those arising in high-risk anatomical sites (floor of mouth, lateral tongue) show greater oxidative damage, consistent with their elevated transformation risk.[4,7]

The translation of these biomarker findings into clinical practice requires addressing several methodological challenges.[19,24] Current studies vary widely in saliva collection methods, assay techniques (colorimetric, HPLC, ELISA), sample processing, and patient demographics, generating heterogeneous reference ranges that limit cross-study comparisons. A consensus standardisation framework — defining collection protocols, assay standards, and minimum reporting criteria — is urgently needed.[9,12] Furthermore, longitudinal studies with long-term follow-up, tracking oxidative marker trajectories alongside clinical and histopathological changes, are relatively scarce; most published data are cross-sectional, limiting causal inference.[8,19] Multicentre prospective cohort studies enrolling diverse OPMD populations are required to establish clinically validated thresholds and define the sensitivity and specificity of individual and panel oxidative markers for predicting malignant transformation.[23,24,28]

## X. FUTURE PERSPECTIVES

### 10.1 Molecular Biomarker Panels

Individual oxidative stress markers — while informative — are limited by variability in assay methods and biological heterogeneity across OPMD subtypes. Multi-marker panels combining MDA, 8-OHdG, TAC, and GSH/GSSG ratio with molecular indicators of cell proliferation (Ki-67), apoptosis (p53, Bcl-2), and epigenetic modification (LINE-1 methylation) may substantially improve predictive accuracy over any single marker.[8,9,23,24] Machine learning approaches applied to multi-omic salivary datasets — integrating oxidative stress markers with proteomic, metabolomic, and microbiome data — represent a promising frontier for building clinically deployable risk prediction algorithms.[23,24]

### 10.2 Point-of-Care Salivary Diagnostics

Advances in microfluidics, lab-on-chip technology, and electrochemical biosensors are enabling development of point-of-care devices capable of quantifying salivary MDA, 8-OHdG, and TAC within minutes, without laboratory infrastructure.[9,12,19] Such devices could be deployed in community dental clinics, primary care settings, and cancer screening programmes in high-risk populations — particularly in South and Southeast Asia where areca nut and tobacco habits drive high OPMD prevalence.[18,19] Standardisation of saliva collection protocols (unstimulated vs. stimulated, time of day, fasting status) and establishment of evidence-based reference intervals will be essential prerequisites for clinical implementation.[12,19]

### 10.3 Antioxidant Therapy and Chemoprevention

The established role of oxidative stress in OPMD pathogenesis provides a compelling rationale for antioxidant-based chemoprevention. Vitamins C and E, β-carotene, lycopene, curcumin, and green tea polyphenols have demonstrated antioxidant efficacy in preclinical models.[23,24,28] Clinical trials of

antioxidant supplementation in OPMD patients have shown variable results; some report clinical resolution or dysplasia regression with lycopene and vitamin E, while others show limited effect. Heterogeneity in patient populations, lesion types, dosing regimens, and outcome measures complicates interpretation.[19,28] Personalised antioxidant therapy — targeting specific identified deficiencies based on individual oxidative biomarker profiles — may prove more effective than uniform supplementation. Polymorphisms in antioxidant enzyme genes (*SOD2, CAT, GPx1*) that affect enzyme efficiency may explain interindividual variation in OPMD progression and identify patients most likely to benefit from supplementation.[8,23,24,28] Rigorous randomised controlled trials with standardised oxidative marker outcomes are needed to establish efficacy and safety for clinical guidelines.[19,28]

## XI. CONCLUSION

Oxidative stress is a central and well-substantiated driver of OPMD initiation, progression, and malignant transformation. The consistent findings of elevated lipid peroxidation products, oxidative DNA damage markers, and reactive nitrogen species alongside depleted enzymatic and non-enzymatic antioxidants across leukoplakia, OSMF, and OLP underscore the biological plausibility and clinical relevance of oxidative imbalance in these disorders. Salivary and serum oxidative stress markers offer clinically viable, non-invasive tools for early diagnosis, risk stratification, disease monitoring, and prediction of malignant transformation as a valuable adjunct to conventional histopathological assessment. Integration of oxidative biomarker evaluation into routine OPMD management may improve early detection of high-risk lesions, enable timely intervention, and ultimately reduce the burden of oral cancer. Future research should focus on standardising assay methods, establishing reference thresholds, and conducting longitudinal trials to validate the prognostic utility of these markers and explore targeted antioxidant therapeutic strategies.

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