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# Salivary Antioxidants Role in Oral Health and Diseases (A Review Article)

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**Abstract**

Background: Saliva is the first defense system of the body through its antioxidant status (total antioxidant capacity), which is either enzymatic or non-enzymatic antioxidants, which block the process of oxidation by neutralizing free radicals; therefore, the objective of this review is to evaluate the role of salivary antioxidant biomarkers in the diagnosis and monitoring of many oral and periodontal diseases and related systemic disorders. Method: We searched for articles published on PubMed and Google Scholar in the last 20 years and then filtered the mints 60 papers according to the following keywords: saliva, total antioxidant capacity (TAC) and oxidative stress (OS). Conclusion: Saliva samples can be beneficial in demonstrating oxidant-antioxidant balance in oral and systemic illnesses and may be a suitable sample type in the diagnosis and monitoring of many pathologies in the body.

# Introduction

Saliva is considered a valid and convenient diagnostic protective biofluid; it is composed by a mixture of the secretion from the major and minor glands. It has physiological significance that has been recognized as a diagnostic fluid for more than two decades (1). Saliva has three primary functions: digestion, lubrication, and to promote healing and protection of mucosa through immunological and enzymatic action (2).
The antioxidant system is the most significant defensive mechanism in saliva against bacteria, viruses, and fungi (2). This method has several advantages, which have led to its use in the treatment of a variety of illnesses. The antioxidant is a substance that ends the chain reaction in the oxidative process caused by free radicals. This activity inhibits the oxidation reaction avoiding cell death and damage (3). Oxidative stress (OS) is an essential cause for many systemic and oral illnesses. It occurs when the intracellular concentration of reactive oxygen radicals increases over the physiological value (4). There are two main sources of free radicals either internal sources (mitochondria and immune defense system) or external sources (cigarette smoke, environmental pollution, radiation, ozone and ultraviolet light) (5) Furthermore; oxidative stress is implicated in a number of clinical conditions, including cancer, rheumatoid arthritis, and neurological conditions (6). There are two types of antioxidants: enzymatic antioxidants such as catalase, glutathione, superoxide dismutase, and peroxidase, and non-enzymatic antioxidants such as beta-carotene, α-tocopherol, ascorbic acid, and flavonoids (6). Uric acid, albumin, glutathione, and ascorbic acid are all found in saliva, uric acid is the most abundant antioxidant in saliva, and the concentrations of ascorbic acid and albumin are greater in saliva than in serum (7), with some antioxidant compounds, ascorbic acid has been demonstrated to function as an endogenous regulator of nitric oxide metabolism (NO). The (NO) regulates endothelial vasodilation and controls vascular inflammation; so ascorbic acid has been used to predict endothelial dysfunction and cardiovascular events (7).

**Salivary antioxidant and dental caries**

Dental caries is one of the most prevalent oral health problems, and prevention of dental caries is one of the most common techniques in many countries; unbalanced levels of oxidants and antioxidants play an important role in the development of tooth decay (3). The crucial function of the salivary peroxidase system in controlling the bacteria in the oral cavity that create dental plaque led to an ecological imbalance that resulted in tooth caries. The mechanism of action of salivary peroxidase is to catalyze the peroxidation of thiocyanate ion (SCN-), which results in the formation of more stable (OSCN-) molecules that impede the development and metabolism of many microorganisms in this way salivary peroxidase slows the progress of caries (8).

**Salivary antioxidants and periodontal disease**

Periodontal disease is an inflammatory disorder caused by the interaction of bacteria and the periodontium. Overproduction of reactive oxygen species (ROS) by periodontal pathogens causes collagen and periodontal tissue degradation; this collagen destruction can be reduced when the antioxidants scavenged ROS, individuals with periodontal disease have increased tissue damage due to free radical generation and a lack of sufficient antioxidant defense (9). Furthermore, low levels of the majority of antioxidants increase the risk of periodontal infection and disease (10).
Exaggerated neutrophil activity may indicate a problem in the inflammatory response in some people (11). The unpaired electrons in free radicals make them highly reactive; these free radicals generate polymorphonuclear neutrophils (PMNS), which cause oxidative killing of bacteria. This results in an immune response to the microorganism, which results in the release of additional

cytokines and the amplification of the inflammatory process (12). Smoking and poor neutrophil function are two factors that contribute to decreased antioxidant capacity; additionally, people with periodontal disease have lower antioxidant capacity in their saliva (13). In patients with periodontal disease, the content of glutathione in serum and gingival crevicular fluid is decrease; this local decrease in antioxidant capacity in gingival crevicular fluid is the larger significance of periodontitis and is linked with tooth and gum destruction (9) .

**Salivary antioxidants and recurrent aphthous stomatitis**

Recurrent aphthous stomatitis (RAS) is a common oral mucosa disorder that affects 20% of the population (14). The clinical features of RSA are recurrent attack and shallow, rounded, discrete, painful oral ulcers (15). The predisposing factors of RAS are stress, trauma, genetic, nutrition, hypersensitivity, immune imbalance and hormonal disturbances that can accelerate the formation of free radicals by the disturbance in the oxidant and antioxidant balance in the living organisms (16). It is suspicious that ROS precipitate in the formation of ulcers; it has the ability to modify cellular macromolecules such as lipid, protein, and DNA, which also, disturbs the cellular function. The oxidation is blocked by antioxidants such as catalase, superoxide dismutase and glutathione peroxidase (17). The powerful antioxidant is the uric acid which scavengers signal oxygen and radicals. It composes around 70% of the total antioxidant of saliva which neutralizes the free radicle and reduces the damage of the cellular components which arise due to the consequence of reaction involving the free radical (14) .

**Salivary antioxidants and oral lichen planus**

Oral lichen planus (OLP) is a chronic inflammation of mucosal tissue and is a cell-mediated immunological condition characterized by cellular degradation. (18). The infiltration of T-lymphocytes into the epithelium causes a local synthesis of cytokines, which causes cellular deterioration which produce oxidative damage sequentially to the mucosal tissue by stimulation ROS formation (19). There are different manifestations of oral lichen planus, as erosive, atrophic, papular, annular, linear reticular and plaque shapes in the buccal mucosa, tongue and gum (20). Oral pain that results from it ranges from a little upsetting to a troublesome pain inhibits the patient's daily function. Also, it is more commonly found in women between forty to sixty years old, in about 2% of people around the world (21). Many different factors could play triggers to cause OLP such as immunological illness, genetic susceptibility, malnutrition, infectious agents and oxidative stress which is the major triggers (22). The metabolic reaction is the first phase in the oxidative stress process, this reaction uses oxygen, which leads to disturbed balance of oxidant/antioxidant reactions in living organisms (6). Keratinocytes, fibroblasts, and numerous inflammatory cells produce reactive oxygen species (ROS), creating an imbalance between oxidants and antioxidants, which can cause lipid peroxidation damage to cell membranes. (23). Malondialdehyde (MDA) is the best and most important investigation of lipid peroxidation in polyunsaturated fatty acid derivatives. Several researches have been reported that a increase concentration of MDA and decrease concentration of antioxidants activities in saliva will lead to increase free radicals during inflammation, which correlated with tissue damage, which may be lead to high risk of disorders like lichen planus (24).

**Salivary antioxidants and temporomandibular joint disorders**

Temporomandibular joint disorder (TMJ): - joint problems are associated with discomfort, articulate noises, muscle soreness, mouth opening restriction, and jaw deviation (25).

This disease can advance chronic and have a severe impact on one's quality of life. Various molecular components, including cytokines, neuropeptides, matrix degrading enzymes, and arachidonic acid catabolites, play a part in this process. (25). TMJ disorders, trauma, mechanical stress, disc disorder and destructive changes can cause the release of free radicals which resulting in to OS and reduction in the defense of antioxidant as well as an increase in the concentration of oxidative biomarkers in serum and saliva such as 8-hydroxyguanosine (8-OHDG), malondialdehyde (MDA), and the oxidant (LDL) which plays a role in initiation of atherogenic and subsequent atherosclerosis (26). Superoxide dismutase (SOD) activity in synovial fluid was significantly reduced in individuals with TMJ problems, which might be related to inadequate clearance of free radicals at the site of inflammation (27). In TMJ disorders, patients with pain had a lower total antioxidant capacity than patients without pain, signifying that there was a higher production of free radicals due to inflammation and pain in muscles or TMJ, and these radicals initiated a cascade of inflammatory reactions in the joint or muscle (28); according to several research, the process of chronic muscular pain suggests that rises in byproducts of oxidative metabolism, particularly in type I muscle fibers, deplete energy supplies and, as a result, activate peripheral pain receptors (29).

**Salivary antioxidants and orthodontic treatment**

Orthodontics is a branch of dentistry that focuses on improving facial and dental esthetics. Aside from this positive point, orthodontic treatment has some risk factors such as tissue damage, treatment incompetence and oral ulcers which is caused by rubbing of the lips and cheeks on brackets (30). Injury to the dental mucosa is a frequent occurrence during orthodontic treatment, as is the discomfort of the labial and buccal mucosa, which are the most common patient complaints related to brackets (31). Another adverse effect of orthodontic therapy is the leakage of the components of orthodontic composite materials into the oral cavity and saliva during therapy, as well as during the polymerization of these materials (32). When these components, such as triethylene-glycoldimekacylate (TEGDMA), methyl methacrylate, and bispherole are released and spread in the oral environment, they can cause a variety of adverse effects in the body, including systemic toxicity, cytotoxicity, allergic reactions, mutagenicity, and carcinogenicity (33). The oxidative/antioxidant balance in saliva varies during orthodontic therapy in healthy people, which leads to the rise of nickel concentration in saliva produced by orthodontic equipment and is responsible for changes in the oxidative condition in saliva (34). Some studies have shown that nutrients, vitamins, and antioxidant compound improve the total antioxidant condition in saliva which has the ability to decrease the oxidative status which reduce the adverse effect of orthodontic therapy (35).

**Salivary antioxidants and cigarette smoke**

Cigarette smoking is a major risk factor for oral diseases such as oral cancer, periodontal disease, alveolar bone loss, and black hairy tongue (36). Tobacco smoking has a direct link with DNA damage; this damage will split the cells, causing a deficiency in the metabolism and duplication of these cells, as well as the emergence of mutations, which are significant components in carcinogenesis (37). Tobacco contains many compounds, including phenols, aldehydes, nitric oxide, and hydrocarbons; all of which directly or indirectly contribute to the production of free radicals. The oxidative stress caused by smoking may lead to alterations in the plasma antioxidant system, with MDA levels increasing and SOD levels decreasing (38). This antioxidants changing of smoking is detectable in saliva (39).

**Salivary antioxidants and oral cancer**

Oral squamous cell carcinoma (OSCC) is one of the 10 most popular cancers worldwide, accounting for 2-4 percent of all new cancer cases (40). Despite recent advances in diagnostic and therapy techniques, the five-year mean survival rate remains quite poor (41). Oral cancer is discovered in two-thirds of patients at advanced tumor stages, when survival reduces to less than 30% and prognosis is unclear (42). The exogenous source of reactive oxygen species (ROS) like tobacco, subsequently leads to oxidative stress (OS). therefore, tobacco products cause increase in production of ROS and free radicals; which have a pathognomonic feature in development of carcinogenesis. They stimulate the mutagenic events through causing DNA damage which lead to degeneration of cellular components. Thus, ROS and free radicals initiate malignant transformation and progression (43). The state of oxidant and antioxidant of the individual affects the pathogenesis, development and progression of premalignant oral lesions like leukoplakia (44), therefore measuring MDA and GSH, which have been established to be an indicator, can be used to determine the extent of oral cancer in the body (40).

**Salivary antioxidants and Insulin dependent diabetic patients**

Diabetes is a widespread systemic disease that affects people all over the world. The diabetic consequences are terrible and well established. The increased generation of ROS has a vital function, particularly in chronic illnesses (45). The strongest responses of ROS alterations in all cellular components restrict the chemical components, leading to lipid peroxidation, which has been documented in diabetic patients with a dispersed capacity of antioxidant defense and ROS generation (46). Endothelial dysfunction has been linked to diabetes, and one endothelial function is involved in nitric oxide (NO) production, which acts as vasorelaxation and a reduction of platelet adhesion. Several investigations have revealed that the substances released from (NO) are reduced in diabetic animals; it is thus hypothesized that diabetes interferes with the production or release of NO by endothelial cell (47). Many growth factors, including insulin-like growth factor (IGF), transforming growth factor (TGF), nerve growth factor (NGF), and epidermal growth factor (EGF) are produced and released by the salivary glands, that the most prevalent growth factor in the body is EGF. When EGF is produced into saliva, it appears to have a variety of systemic effects on the body. Some investigations have found that diminished growth factor secretion in saliva in diabetic animal models due to the oxidative stress, and the reduced the antioxidant capacity of saliva (48). This antioxidant ability arises from the significant function of NO and EGF in saliva (49). Some researchers suggest that in diabetic patients, with fasting salivary glucose levels were significantly elevated, which led to a decrease in TAC in saliva (50), while the levels of salivary total protein were found to be higher in diabetic patients when compared to healthy people; albumin is a protein antioxidant that contributes significantly to antioxidant plasmatic barriers (51). One of the significant observations for diabetes is the glycemic status in saliva (50).

**Salivary antioxidants and chronic kidney diseases (CKD) in children**

This diseases is distinguished by a gradual decrease in glomerular filtration rate (GFR) due to oxidative stress which play an important role in CKD (52). Many studies have shown that the mechanism of Renin-Angiotensin system has a significant effect in controlling blood pressure. Also, it contributes to the pathophysiology of inflammation and the development of CKD. When many inflammatory processes have the ability to express angiotensin II; that the natural killer cells, and monocytes are formed. Angiotensin II can cause oxidative stress via an oxidative burst and can promote phagocyte activity and chemotaxis. As

well as, to its impact on its development, angiotensin II induces inflammation and aggravates the process itself (52).The antioxidative barrier may be reinforced and uric acid levels increased in the saliva of children with CKD due to the excess production of the Renin-Angiotensin-Aldosterone system, which disrupts mitochondrial function and subsequent activation of NOX (NADPH oxidase);which is the main source of ROS in the cells (53) .Some investigations found that higher activity of salivary peroxidase and superoxide dismutase, as well as uric acid and albumin concentrations, resulted in improved antioxidant defense in CKD patients' saliva (54).

**Salivary antioxidants and cerebral palsy**

Cerebral palsy is a non-progressive disease characterized by abnormalities in mobility and posture caused by central nervous system damage during brain development. Those individuals with a higher prevalence of dental disease due to inability to complete oral hygiene, including dental caries, periodontitis, malocclusion, and bruxism, as well as drooling in those patients as a result of swallowing difficulties (55). The crucial role in the etiology of neurological illnesses is oxidative stress, which plays a vital role in the beginning and progression of many inflammatory degenerative diseases owing to an imbalance in the levels of ROS and antioxidants (24). Children with cerebral palsy have lower total antioxidant status (TAS) levels in their saliva than normal children. The level of sialic acid (SA) in saliva which is an essential component of glycoproteins is greater in children with cerebral palsy which may be due to the greater breakdown of glycoproteins by hydrolytic enzymes. Also, a prior study observed that children with cerebral palsy had greater levels of total protein and sialic acid in their saliva. This may be due to an inverse relationship between TAC and the oxidants in those children.(56).

**Salivary antioxidants and Crohn's disease**

Crohn's disease (CD) is a chronic inflammatory condition that can affect any region of the gastrointestinal system, but most often affects the terminal ileum and proximal colon. The development of fistulas, intestinal strictures, and intra-abdominal abscesses complicates the disease's progression in half of the patients (57). The complex etiology of CD is unclear; nevertheless, numerous features, including the immunological system of the host and genetics, may act a key part in disrupting intestinal homeostasis, resulting in a deregulated inflammatory response of the G.I.T. (58). Several investigations have found an increase in reactive oxygen species and a reduction in antioxidant levels in CD patients' intestinal mucosa and plasma (59). Glutathione peroxidase (GPx) and superoxide dismutase (SOD) are two key intracellular antioxidant enzymes that protect cells from the damaging effects of ROS (60). Patients with CD show qualitative alterations in salivary content, as well as asymptomatic orofacial granulomatosis (61). The examination of saliva for oxidative stress indicators that reduce SOD and GPx activity in entire saliva in CD patients may be of significant therapeutic relevance in determining the body's redox state (62). Saliva is a diagnostic fluid that does not require any invasive procedures and is used to evaluate biomarkers produced during CD disease; these specialized biomarkers linked with chronic diseases and its seriousness may have a significant effect on the early detection of the disease (63).

## Conclusion

Saliva is a potential biofluid for biomarkers development due to the simplicity and safety of collection, as well as the availability of measurable substrate for identifying physiological and pathological conditions in the human body. Saliva samples can be beneficial in demonstrating oxidant-antioxidant balance

in oral and systemic diseases and may be a suitable sample type in the diagnosis and monitoring of many pathologies in the body**.**

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