# EFFECT OF NATURAL ANTIOXIDANTS ON SALIVARY BIOMARKERS OF OXIDATIVE STRESS AND INFLAMMATION IN CHILDREN AT HIGH RISK OF CARIES

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## Abstract

Oxidative stress is considered as an imbalance between the production of reactive oxygen species and their elimination by defense mechanisms, which can lead to chronic inflammation. The inflammation caused by oxidative stress is the cause of many chronic diseases. The use of natural products provides an alternative in the construction of new natural antioxidants.

The direct contact of saliva with oral lesions, as well as its simple availability, determine its potential use as a diagnostic medium for early detection of oral diseases. Isolation of appropriate salivary biomarkers allows for timely identification of patients at high risk of caries. Such biomarkers can also be used to assess the status of orally healthy individuals, including when monitoring patients over time.

The proposed review of the specialized dental literature aims to summarize the influence of natural antioxidants on salivary biomarkers of oxidative stress and inflammation in children at high risk of caries.

There are few research on the influence of natural antioxidants on salivary biomarkers is due to the nature of current diagnostics of carious lesion, which is mainly based on visual examinations, optical devices, tactile assessments and radiographs. A review of the literature on different salivary biomarkers can be used to increase the sensitivity of carious lesion detection, as well as to improve strategies for their prevention.

***Keywords:*** *natural antioxidants, salivary biomarkers, childhood caries, reactive oxygen species, caries prevention*

## Introduction

Dental caries is a multifactorial disease that develops with the participation of several groups of factors – enamel structure, microorganisms, fermentable carbohydrates, time and saliva. These factors act simultaneously and mutually. Saliva is the main component of the liquid oral environment. It participates in the maintenance of oral homeostasis. With its numerous functions and specific composition, saliva has an important role in the prevention and treatment of oral diseases. Saliva testing can be used to identify salivary biomarkers of oxidative stress and inflammation in children with carious lesions (1). In addition to diagnosis, salivary biomarkers are used to monitor various diseases. Due to the easy and non-invasive collection of saliva, salivary tests can be used as a diagnostic tool in childhood.

Oxidative stress is considered as an imbalance between the production of reactive oxygen/nitrogen species (ROS/RNS) and their elimination by defense mechanisms, which can lead to chronic inflammation. The inflammation caused by oxidative stress is a cause of various chronic diseases (2). The imbalance between cellular antioxidants and the produced reactive free radicals, such as reactive oxygen species (ROS) or reactive nitrogen species (RNS), is known as oxidative stress (3). Free radicals are molecules or ions that have unpaired electrons in their atomic orbitals (4). An imbalance in the production of these unpaired electrons and antioxidants causes oxidative stress (5, 6). Antioxidants are substances that prevent, inhibit or reduce oxidative processes (7, 8).

This review of the specialized dental literature aims to summarize the influence of natural antioxidants on salivary biomarkers of oxidative stress and inflammation in children at high risk of caries.

Antioxidants

There are two categories of antioxidants – natural and synthetic (Figure 1). Synthetic antioxidants are not the main choice for therapy because they have proven harmful and carcinogenic

effects (4). The use of natural products provides an alternative in the construction of new natural antioxidants.

Natural antioxidants are divided into endogenous and exogenous. Endogenous are non-enzymatic and enzymatic. Enzymatic are divided into primary and secondary. Primary are catalase, superoxide dismutase (SOD), glutathione peroxidase (9). Secondary are glucose-6-phosphate dehydrogenase and glutathione reductase. Non-enzymatic are divided into metal-binding proteins and low molecular weight. Exogenous are vitamins, minerals, carotenoids and polyphenols (10).

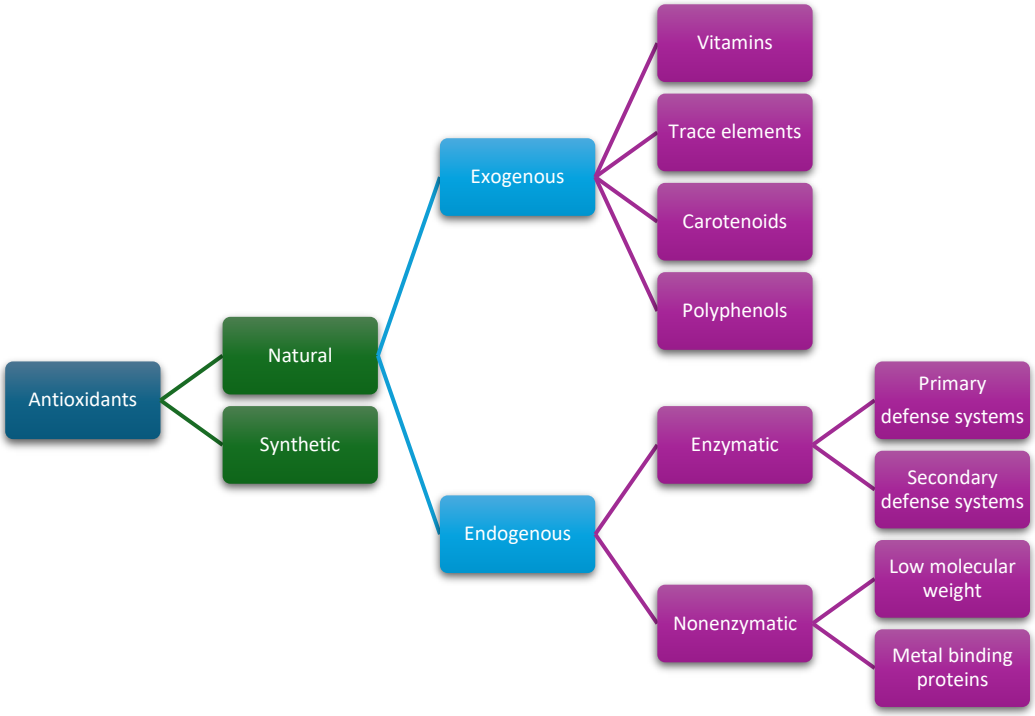


Figure 1. Classification of antioxidants

Antioxidant systems are complex systems, with an important function being protection against the effects of ROS (1). Both enzymatic and nonenzymatic antioxidant systems are present in saliva. Glutathione peroxidase, catalase and SOD are examples of enzymes with SOD being the major antioxidant enzyme (11, 12). This enzyme catalyzes the radical conversion of superoxide anions to hydrogen peroxide and oxygen (13).

Examples of nonenzymatic antioxidants are uric acid and glutathione, which together constitute the total antioxidant capacity (TAC) (14). Enzymes involved in antioxidant defense can degrade ROS and protect the body from damage. The reductase enzymes, glutathione reductase (GTR) and thioredoxin reductase (TRR), play a role in the secondary antioxidant system. They are responsible for the constant generation of reduced nicotinamide adenine dinucleotide phosphate (NADPH), which is used as a cofactor for the aforementioned enzymes to regenerate antioxidants (such as glutathione and thioredoxin) that neutralize ROS production (15). Nonenzymatic antioxidants are compounds that can counteract free radicals without the intervention of enzymes. Nonenzymatic antioxidants are endogenous and exogenous. Melatonin, known as N-acetyl-5-methoxytryptamine, is one of the antioxidants that easily penetrate cell membranes and the blood-brain barrier, thus protecting cell membranes from lipid peroxidation (16). The amino acid tryptophan is the source of this hormone melatonin. Melatonin is called a terminal antioxidant because it does not enter the redox cycle (17). Melatonin can be oxidized to form end products, but it cannot return to its original state. Glutathione possesses antioxidant properties of its thiol group, which can be reversibly oxidized and reduced (18). Glutathione is a cellular antioxidant due to its importance in maintaining the redox state of the cell and its high concentration. Glutathione is a peptide that is produced in cells from amino acids and can directly reduce ROS (19). Coenzyme Q10 (2,3-dimethoxy-5-methyl-6-polyisoprene

parabenzoquinone), or often called ubiquinone, is generated by isoprenoid oligomerization via the mevalonate pathway (20). Ubiquinone is an antioxidant molecule that is fat-soluble, protects the body from lipid peroxidation and oxidative damage. It can scavenge some ROS and regenerate other oxidized antioxidants (21).

Exogenous antioxidants must be taken regularly, since the human body does not produce them, they are synthesized in plant cells or microorganisms. Vitamins, flavonoids and carotenoids are exogenous substances that come with food and exhibit antioxidant activity. Dehydroascorbic acid (DHA) can be obtained by two-electron oxidation of vitamin C or ascorbic acid (AA). AA is found in tomatoes, pineapple, watermelon and all citrus fruits. The main function of AA is to scavenge ROS in the form of $O_2$, $H_2O_2$, organic peroxides, HClO or OH (22). Vitamin E is a fat-soluble vitamin that protects cells from damage caused by free radicals. Flavonoids are compounds with high antioxidant activity, as they are highly effective in reducing ROS, such as superoxide anions and peroxyl radicals, through the hydrogen atom transfer (HAT) mechanism (23). Flavonoids chelate some metal ions and block the formation of free radicals. An example of such a flavonoid is quercetin, which can be a chelator and stabilizer of iron (24). Carotenoids have the biological activity of scavenging ROS. One of the most abundant carotenoids is β-carotene, found in carrots, pumpkins, and mangoes (25). Flavonoids, of plant origin, are used as traditional therapeutic agents with proven bioactivity. Flavonoids, as secondary metabolites derived from plants, prevent the development of free radicals. The presence of hydroxyl groups in the structure of flavonoids becomes a determining factor for the scavenging of free radicals. The presence and location of hydroxyl groups in the structure of flavonoids are key factors for their antioxidant activity. Flavonoids are promising natural compounds with potential health benefits (4).

Biomarkers in saliva

The direct contact of saliva with oral lesions, as well as its easy availability, highlight its potential use as a diagnostic medium for the detection of oral diseases. The discovery of suitable salivary biomarkers allows the early identification of patients at high risk of caries. Such biomarkers can also be used to assess the status of orally healthy individuals, including in the monitoring of patients over time.

Oxidative damage, a consequence of oxidative stress, is determined by the increased concentration of ROS and RNS, associated or not with reduced activity of antioxidant systems (26). According to Ghezzi (27), biomarkers related to oxidative stress are divided based on their biological significance into biomarker types 0, 1, 2, 3 and 4 (Table 1).

Table 1. Biomarkers related to oxidative stress according to Ghezzi (27).

| Type 0 | Type 1 | Type 2 | Type 3 | Type 4 |
|---|---|---|---|---|
| • Direct measurement of ROS | • Malondialdehyde (MDA)<br>• 8-hydroxydeoxy-guanosine (8-OHdG)<br>• Isoprostane<br>• Oxidized low-density lipoprotein (oxLDL)<br>• Hydroxynonenal (HNE)<br>• Protein carbonyls<br>• Ischemia-modified albumin (IMA) | • Uric acid<br>• Allantoin<br>• Hypochlorous acid (HOCl) | • Superoxide dismutase (SOD)<br>• Catalase ( CAT)<br>• Glutathione peroxidase (GPx)<br>• Paraoxonase 1 (PON1)<br>• Xanthine oxidase (XO)<br>• Dual oxidase ( DUOX)<br>• Total antioxidant capacity ( TAC)<br>• Vit E, Vit C<br>• Billirubin | • Genetic factors mutations |

Type 0 biomarkers directly measurement ROS in vivo in patients. Type 1 biomarkers are the most commonly used indicators of oxidative stress, represented by oxidized lipids, proteins, or

nucleic acids and their bases. Type 2 biomarkers are indicators of the activation of biochemical pathways that can lead to the formation of ROS. Type 3 biomarkers are host factors, such as low molecular weight antioxidants and antioxidant enzymes, while type 4 biomarkers measure genetic factors and mutations that could alter an individual's susceptibility to oxidative stress (27). Among the major markers of oxidative damage are malondialdehyde (MDA), a stable end product of membrane lipid peroxidation, and 8-hydroxy-deoxyguanosine (8-OHdG) (11). TAC is commonly used as a marker of salivary antioxidant capacity, while MDA reflects oxidative damage (28).

SOD

Among the biomarkers of the antioxidant system analyzed in a systematic review by Martins et al. (29), TAC and SOD showed higher levels in the group of children with dental caries compared to those without caries, regardless of the age range and gender evaluated. A similar trend was observed for the concentrations of total proteins in saliva. On the other hand, for the biomarker of oxidative damage MDA, salivary flow, pH, buffer capacity and calcium concentrations were significantly lower in the group of children with caries.

TAC

The caries process alters the balance between ROS production and antioxidant systems. A shift in the balance in favor of oxidative damage is associated with the development of disease (30). The antioxidant response of saliva varies in different oral diseases. TAC has been shown to be reduced in periodontal disease (31) but increased in dental caries (32). Furthermore, changes in salivary ROS concentrations may impair the antibacterial activity of saliva and create conditions for the initiation of caries (33).

A strong positive correlation between increased activity of antioxidant systems (TAC, uric acid and SOD) and different stages of dental caries progression was described in a study by Araujo et al. (34) in children. The higher the severity of caries, the higher the activity of the antioxidant system in saliva, with a subsequent decrease in oxidative damage in saliva or MDA. These data support the hypothesis that the organism may develop an adaptive response to the disease and that the reduction in oxidative damage in saliva in children with carious lesions may be a consequence of increased activity of antioxidant systems, both enzymatic (SOD) and non-enzymatic (35) .

Concentrations of salivary protein are increased in children affected by caries (1, 34). Increased protein concentrations are observed in children with a higher incidence of Streptococcus mutans, suggesting a response to the infectious nature of advanced caries, as opposed to the presence of the disease in its early stages (36).

TAC provides information about the balance between the oxidant and antioxidant systems. High antioxidant levels contribute to the reduction of oxidative damage. TAC in saliva increases with the severity of carious lesions. TAC in saliva of children with carious lesions is higher than in children without. Higher severity of carious lesions increases the activity of the salivary antioxidant system, which leads to a decrease in oxidative damage in saliva (34). In a study by AlAnazi et al. (37) found a decrease in TAC in saliva of children with early childhood caries after treatment of carious processes.

8-Isoprostane

Another biomarker in saliva for assessing oxidative stress is 8-isoprostane. After treatment of carious lesions, a decrease in the concentration of 8-isoprostane in saliva is observed. The physicochemical properties of saliva also improve (38). Isoprostanes are stable substances that are found in all biological fluids and can be easily assessed. They are produced as end products of lipid peroxidation in membranes and lipoproteins.

Cytokines

Sharma et al. (39) studied the levels of inflammatory cytokines (IL-6, IL-8 and TNF-α) in saliva samples of children with early childhood caries (ECC) and assessed the variations in their levels before and after treatment. The levels of IL-6, IL-8 and TNF-α in saliva were higher increase treatment and decreased after treatment. The levels of these cytokines were related to the severity of the carious process. IL-6 is a major anti-inflammatory cytokine, secreted mainly by T cells and

macrophages and leads to the stimulation of the immune response. IL-8 is a chemokine produced by macrophages and other cell types, such as epithelial and endothelial cells. This cytokine is also known as neutrophil chemotactic factor, whose main function is chemotaxis to target cells, along with the induction of phagocytosis. Tumor necrosis factor alpha (TNF-α) is a cell signaling protein involved in systemic inflammation, which constitutes the acute phase response. It is produced mainly by activated macrophages with a major role in regulating immune cells. The levels of these inflammatory cytokines are increased in periodontal diseases. There are few reports available that show an increase in inflammatory cytokine levels in the carious process (40). Studies by Menon et al. And Seyedmajidi et al. Discuss the increased levels of IL-6 or IL-8 in saliva in children with carious lesions (41, 42).

Various studies have found promising perspectives regarding the important role of the potential therapeutic use of oxidative stress markers. Table 2 presents the systematic results of studies on TAC, MDA, SOD, IL-6, IL-8 and TNF-α.

Table 2. Systematic researches on TAC, MDA, SOD, IL-6, IL-8 and TNF-α.

| Authors | Results |
|---|---|
| Sharma V et al., 2017 | Saliva levels of IL-6, IL-8 and TNF-α are significantly higher in patients with ECC and decrease significantly after treatment |
| AlAnazi GS et al.,2018 | Reduction of TAC in the saliva of children with early childhood caries after treatment of carious processes. |
| Araujo HC et al., 2020 | Caries severity has a direct effect on the activity of antioxidant systems and TAC |
| Poimenidou AA et al., 2025 | Physicochemical improve after caries treatment. A reduced concentration of the oxidative stress factor 8-isoprostane is observed in saliva after caries treatment. |
| Martins JR et al., 2022 | TAC levels are higher in children affected by dental caries<br>MDA levels were lower in the affected by dental caries<br>SOD levels were higher in the affected by dental caries |

## Conclusion

The levels of oxidative stress biomarkers and salivary parameters are altered in children with developing caries. Biomarkers of the antioxidant system (TAC and SOD) and total protein concentration are higher in children affected by the disease. On the other hand, the biomarker of oxidative damage in saliva (MDA) and salivary parameters such as flow rate, pH, buffer capacity and calcium show reduced values in children with carious lesions. Therefore, it can be assumed that caries disease has an influence and leads to changes in the levels of oxidative stress biomarkers (29).

Various factors influence oxidative stress markers, free radicals and antioxidants. Future studies should focus on clarifying the bidirectional relationship between them and oral diseases.

There are few research on the influence of natural antioxidants on salivary biomarkers is due to the nature of current caries diagnostics, which is primarily based on visual examinations, optical caries detection devices, tactile assessments, and radiographs. A review of the literature on various salivary biomarkers has the potential to increase sensitivity in the detection of early caries lesions and contribute to the development of new prevention strategies.

Statement for Potential Conflicts of Interest

The autors declare that they have no potential conflicts of interest related to this article.

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