Dental Journal
Majalah Kedokteran Gigi

Dental Journal
(Majalah Kedokteran Gigi)
2024 June; 57(2): 74–79

Review article

Review of salivary antioxidants and their barriers

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ABSTRACT

Background: *Oxidative stress results from the imbalance between reactive oxygen species (ROS) and cellular antioxidant defenses. Oxidative stress can cause damage to cellular structures such as cell membranes, lipids, proteins, lipoproteins, and deoxyribonucleic acids when free radicals are present in excess. Antioxidant mechanisms protect tissues against oxidative stress by decreasing free radical levels in cells through the inhibition of activities or expression of free radical-generating enzymes.* ***Purpose:*** *The purpose of this paper is to discuss the role of antioxidants in protecting cells from the harmful effects of ROS, particularly in the context of oral mucosa, and to clarify which molecules disrupt the pathway of these antioxidants.* ***Review:*** *Salivary peroxidase, catalase, superoxide dismutase, and glutathione reductase are enzymatic salivary antioxidants, and uric acid, reduced glutathione, albumin, and lactoferrin are non-enzymatic antioxidants. Both types of antioxidants regularly donate an electron to free radicals to reduce their levels in cells.* ***Conclusion:*** *Antioxidant activities may be disrupted by signaling mechanisms resulting from barrier regulations observed in tissue. The increased expression of malondialdehyde is an indicator of disrupted antioxidant barriers.*

Keywords: *antioxidants; malondialdehyde; oxidative stress; reactive oxygen species; saliva*
Article history: *Received 11 July 2023; Revised 5 October 2023; Accepted 18 October 2023; Published 1 June 2024*

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INTRODUCTION

Antioxidants play a key role in protecting cells from the harmful effects of reactive oxygen species (ROS). When ROS are present in excess, antioxidant systems can become exhausted and less effective, resulting in oxidative stress-mediated damage to cells. As a result of oxidative stress-mediated injury, ROS can cause damage to lipids, proteins, and DNA, which alters the structure and functioning of cells, causing diseases to develop.[1]

In the oral cavity, ROS can mediate damage to the periodontium, causing periodontitis.[2] The oral cavity is unique in that it is one of the only organs that is constantly exposed to different factors that produce ROS, such as tobacco smoke, microorganisms, and dietary components. Saliva is therefore crucial because it contains numerous antioxidants that protect against the overproduction of ROS in the oral cavity. Examples of ROS include radical species such as hydroxyl and superoxide anions and non-radical species such as hydrogen peroxide, hypochlorous acid, and peroxynitrite.[3]

Antioxidants counteract free radicals by reacting directly with them, which involves donating or accepting an electron, and also indirectly by inhibiting enzymes responsible for generating free radicals. Saliva contains both enzymatic and non-enzymatic antioxidants as well as phenols, which play an antioxidant-like role. However, there are molecules that can act as a barrier to these antioxidants, preventing them from completing their role of counteracting ROS.[4] This creates a major problem, as the antioxidants become less effective, thereby allowing ROS to cause more damage to the oral cavity and, to a larger extent, the human body. Currently, few published studies have investigated the molecules that function as barriers to antioxidants, and studies explicitly identifying these molecules are lacking. It is therefore imperative that adequate research is conducted to identify these molecules and their mechanisms to aid in developing treatments that

DOI: 10.20473/j.djmkg.v57.i2.p74–79

can help to disarm them. The purpose of this review is to highlight the different types of antioxidants found in saliva and to clarify which molecules disrupt antioxidant pathways. This narrative review focuses on both enzymatic and non-enzymatic antioxidants. The studies used as the basis of this review are original research studies and other review studies published in the past decade that have explored the specific roles of each of the antioxidants found in saliva and molecules that may work antagonistically to these antioxidants.

REVIEW

Enzymatic antioxidants

One major enzymatic antioxidant in saliva is superoxide dismutase (SOD). There are three variations of this enzyme (isoenzymes). They are responsible for catalyzing the reaction by which molecular oxygen and the ROS, hydrogen peroxide, are produced from superoxide anions, which create more ROS (dismutation reaction; Figure 1). This further prevents a harmful reactive nitrogen species (RNS), the superoxide nitrate ion, from being formed because superoxide anions can be converted into superoxide nitrate ions if not neutralized early enough. The hydrogen peroxide formed from the superoxide anion dismutation reaction is also a type of ROS; however, a second enzymatic antioxidant in saliva, catalase, is responsible for its inactivation. Catalase achieves this by reducing the amount of hydrogen peroxide, which produces water, and to protect against its own oxidative inactivation by hydrogen peroxide, the catalase enzyme binds to nicotinamide adenine dinucleotide phosphate (NADPH) during this process.[5] Hydrogen peroxide is also eliminated by a third enzymatic antioxidant found in saliva, glutathione peroxidase. This antioxidant is responsible for the reduction of hydrogen peroxide. For this reaction to occur, reduced glutathione is oxidized into glutathione disulfide. In this process, hydrogen peroxide cannot undergo the Fenton reaction to produce the very reactive hydroxyl radical.[6] Another enzymatic antioxidant, glutathione reductase, regenerates the reduced glutathione required by glutathione peroxidase, as mentioned previously. It is important to note that catalase at low concentrations acts in a similar manner to peroxidase, and one of the SOD isoenzymes also exhibits peroxidase-like properties. Peroxidase is a fourth enzymatic antioxidant present in saliva, and it is considered the most important of the salivary enzymes. The salivary peroxidase system has several counterparts: peroxidase, myeloperoxidase, thiocyanate ions (SCN^-), and hydrogen peroxidase.[5,7] One of its roles is to reduce hydrogen peroxide into water while oxidizing ions such as bromide, thiocyanate, and iodide ions, thus allowing the level of hydrogen peroxide being secreted by the salivary gland by way of excretion from bacteria and leukocytes to be controlled.[8] In addition, it catalyzes the oxidation of chloride ions, forming hypochlorous acid, which produces chloramines. Chloramines exhibit antibacterial activity and thus protect the oral cavity.[4,5]

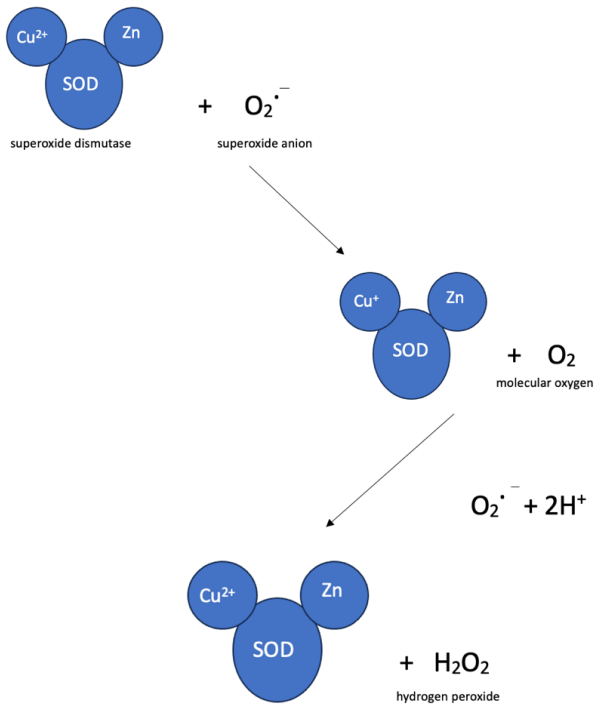

Figure 1. Superoxide dismutase mechanism that produces hydrogen peroxide and molecular oxygen from superoxide anions.

Non-enzymatic antioxidants

Similar to the role of peroxidase as the most important enzymatic antioxidant, uric acid is the most important non-enzymatic antioxidant. Studies indicate that uric acid accounts for more than 85% of the total antioxidant capacity of both stimulated and unstimulated saliva in humans.[5,9] It reacts with hydroxyl radicals, superoxide anions, hydrogen peroxide, and peroxynitrite by donating an electron to these species, decreasing their levels, and protecting cells from oxidative stress (Figure 2).[10] Peroxynitrate is a RNS that uric acid preferentially reacts with because uric acid is responsible for counteracting the RNS found in saliva.[11] Additionally, uric acid may be responsible for maintaining SOD levels, an enzymatic antioxidant. The second major non-enzymatic antioxidant found in saliva is ascorbic acid or vitamin C. Ascorbic acid protects cell membranes from free radical-mediated lipid peroxidation by preventing aqueous peroxyl radicals from oxidizing lipids found within the cell membranes (Figure 3).[12] Ascorbic acid is a water-soluble and extracellular antioxidant, and it is therefore able to react with and fight against free radicals before lipid-soluble antioxidants gain access to them; ascorbic acid is therefore efficient. Albumin is a protein found in saliva that serves as another non-enzymatic antioxidant. It is able to bind to different molecules such as metal ions, including iron and copper. The binding of albumin to

DOI: 10.20473/j.djmkg.v57.i2.p74–79

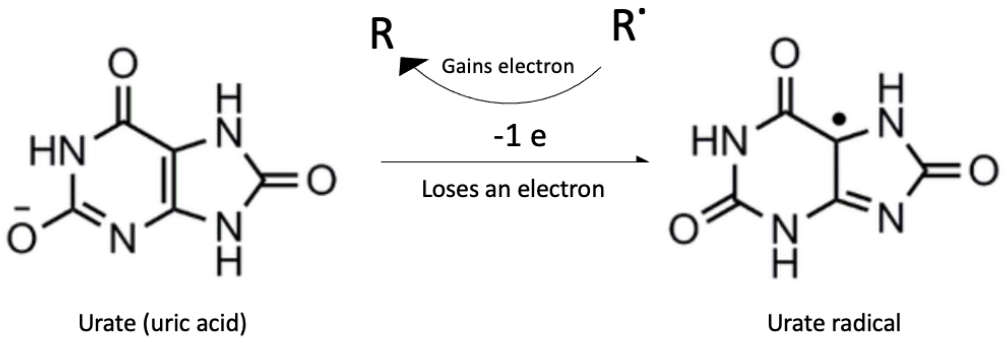

Figure 2. Uric acid mechanism for donating an electron to a free radical.

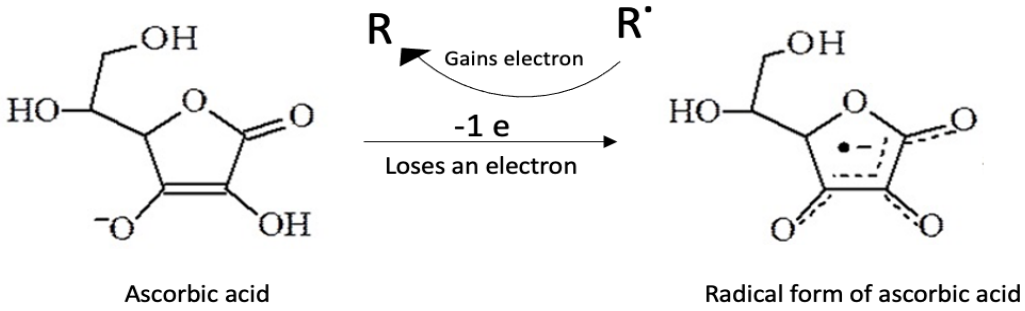

Figure 3. Ascorbic acid mechanism for donating an electron to a free radical.

Table 1. Enzymatic and non-enzymatic antioxidants of saliva and their role in oral mucosa

Enzymatic antioxidants	Superoxide dismutase	Superoxide dismutase is an enzyme that catalyzes the dismutation of superoxide radicals into hydrogen peroxide and oxygen. It acts as the first line of defense against superoxide radicals, which are highly reactive and potentially damaging molecules. Superoxide dismutase helps prevent oxidative stress and tissue damage in the oral mucosa.
	Catalase	Catalase is an enzyme that converts hydrogen peroxide into water and oxygen. It plays a crucial role in neutralizing hydrogen peroxide, a reactive oxygen species that can cause cellular damage and oxidative stress. Catalase helps maintain a balanced redox environment in the oral mucosa.
	Glutathione peroxidase	This enzyme catalyzes the reduction of hydrogen peroxide and organic hydroperoxides using reduced glutathione as a cofactor. By doing so, it protects cells from oxidative damage caused by peroxides. Glutathione peroxidase contributes to maintaining cellular integrity in the oral mucosa.
Non-enzymatic antioxidants	Glutathione	Glutathione is a tripeptide molecule composed of cysteine, glutamate, and glycine. It acts as a major intracellular antioxidant and plays a key role in maintaining redox balance. Glutathione scavenges free radicals, detoxifies harmful compounds, and helps protect cells from oxidative stress in the oral mucosa.
	Vitamin C (ascorbic acid)	Vitamin C is a water-soluble antioxidant that scavenges reactive oxygen species and helps regenerate other antioxidants, such as vitamin E. It contributes to collagen synthesis, supports wound healing, and enhances the immune response in the oral mucosa.
	Vitamin E (tocopherols and tocotrienols)	Vitamin E is a fat-soluble antioxidant that protects cell membranes from lipid peroxidation by neutralizing lipid-derived free radicals. It helps maintain the integrity of oral mucosal cells and supports overall tissue health.
	Carotenoids	Carotenoids, such as beta-carotene, lutein, and zeaxanthin, are pigments found in various fruits and vegetables. They have antioxidant properties and play a role in quenching free radicals generated by sunlight and other environmental factors, thus helping to protect the oral mucosa from oxidative damage.

DOI: 10.20473/j.djmkg.v57.i2.p74–79

metal ions prevents the participation of these ions in the Fenton reaction, which can generate the highly reactive and dangerous hydroxyl radical. The ligand-binding capacity of albumin is therefore one of its antioxidant properties. Additionally, albumin acts as an antioxidant because it is able to scavenge ROS such as hypochlorous acid and hydroxyl radicals, thereby preventing them from harming macromolecules.[13] Some other non-enzymatic antioxidants contained in saliva are tocopherol and lactoferrin, which are of less significance when compared with the roles of uric acid and ascorbic acid in saliva.

Specific roles of enzymatic and non-enzymatic antioxidants in the oral mucosa

Enzymatic and non-enzymatic antioxidants collectively act as a defense system against oxidative stress and free radicals in the oral mucosa. They help prevent cellular damage and maintain the functional integrity of oral tissues, including the epithelial lining and connective tissues. Antioxidants contribute to the healing process of oral wounds and ulcers by reducing inflammation and promoting tissue repair. They protect oral mucosal cells from oxidative damage caused by environmental factors, such as ultraviolet radiation, pollutants, and toxins. Antioxidants also support the immune system in responding to infections and maintaining oral health. Thus, enzymatic and non-enzymatic antioxidants play vital roles in safeguarding the oral mucosa from oxidative stress, promoting tissue repair, and maintaining overall oral health (Table 1).

Barriers to antioxidants

When hydrogen peroxide is produced in excessive amounts, it causes the age-related reduced activity of SOD.[14] Hydrogen peroxide, in this case, serves as a barrier to SOD, as it results in the enzyme's deactivation when present in excess. In addition, SOD's active center can be deactivated by superoxide radicals when they are present in excessive amounts.[15,16] This line of antioxidant defense, therefore, becomes exhausted and less efficient at protecting cells from ROS. It has also been observed that *Aggregatibacter actinomycetemcomitans*, an oral pathogen, secretes a leukotoxin that can bind to the copper and zinc isozymes of SOD, inhibiting its activity against ROS.[17,18] This indicates that other oral pathogens might produce molecules that serve as defense mechanisms to disrupt the antioxidant barrier. Research into these molecules can help develop treatments that prevent antioxidant levels from becoming depleted, thereby strengthening the antioxidant barrier. Another molecule of interest that relates to the disruption of the antioxidant pathway is malondialdehyde (MDA). The increased concentration of MDA in tissue is indicative of antioxidant barrier disruption.[14] Research is required to investigate the mechanism of MDA in disrupting the antioxidant pathway and to determine other molecules capable of acting as a barrier to antioxidants. If such molecules are scientifically verified to be antagonistic to antioxidants, one possible method of treatment for disease caused by oxidative stress is to decrease the levels of these molecules while also increasing antioxidant levels through methods such as dietary intake. Another angle for research to identify barriers to antioxidants is to determine the molecules present in saliva that are similar in structure or function to known inhibitors of enzymatic antioxidants. If this is achieved, the mechanism behind antioxidant barrier depletion can be used to guide treatments for protecting cells against oxidative stress.

DISCUSSION

Antioxidants and barriers to antioxidants in saliva as indicators of oxidative stress

The ability to measure antioxidants, whether by measuring the activity of a specific antioxidant or the total antioxidant capacity of a cell, is vital because the resulting data can be used as a biomarker of oxidative stress. Lower-than-expected antioxidant activity, for instance, would indicate that the antioxidant barrier has been disrupted, thereby signaling that oxidative stress may be occurring within that cell.[19]

Recent studies have measured the levels of specific antioxidants in saliva, such as glutathione peroxidase, SOD, uric acid, ascorbic acid, and ceruloplasmin, in smokers and non-smokers. All three studies determined that the level of the aforementioned antioxidants were lower in smokers.[20–22] Similarly, studies have measured the salivary total antioxidant capacity of smokers and non-smokers, revealing once again that the antioxidant capacity was lower in smokers.[23–25] Smoking is known to produce ROS, and when there is an overproduction of ROS, antioxidant levels are likely to be depleted, thereby producing oxidative stress.[26–31] The expected lowering of antioxidants during oxidative stress make measuring antioxidant levels a suitable marker for determining the degree of oxidative stress and, by extension, the stage of the diseases associated with oxidative stress, such as periodontitis. An example of this is the decreased levels of uric acid and glutathione in individuals with periodontitis compared with healthy controls.[4,16,18] A healthy person is more likely to have a higher level of antioxidants than a person with periodontitis.[32,33] This reveals the suitability of using antioxidants in saliva as a diagnostic marker to determine the stage of oxidative stress in a person's oral cavity, providing an indicator of the severity of deterioration in a patient's periodontal condition.

The barrier molecules that oppose antioxidants in saliva are currently not widely studied. Once the barrier molecules that disrupt the antioxidant pathway are more clearly identified in research, their levels could be measured to help determine the stage of oxidative stress in patients in relation to the levels of antioxidants being used. A large number of barrier molecules would be indicative of an increase in oxidative stress, and a relatively small number of

DOI: 10.20473/j.djmkg.v57.i2.p74–79

antioxidants would be indicative of an increase in oxidative stress. These concepts can be applied to the development of treatments for patients with periodontitis and other diseases associated with oxidative stress. Because a relatively small number of antioxidants is associated with an increase in oxidative stress, a possible form of treatment for this condition would be to increase the intake of antioxidants; for example, by increasing the consumption of fruit in the patient's diet.[34] Similarly, since an increase in barrier molecules is associated with an increase in oxidative stress, another possible form of treatment would be to decrease the levels of molecules that form a barrier to antioxidants. However, the mechanisms by which these barrier molecules disrupt the antioxidant pathway would need to be studied for such treatments to be effective, thus emphasizing the need for research to address the gap in knowledge concerning these barrier molecules.

Conclusion

Both enzymatic and non-enzymatic antioxidants present in saliva work to protect the oral cavity against ROS to prevent oxidative stress-mediated injuries. The main enzymatic antioxidants found in saliva are SOD, catalase, glutathione peroxidase, glutathione reductase, and peroxidase; peroxidase is considered the most important. The main non-enzymatic antioxidants are ascorbic acid, albumin, tocopherol, lactoferrin, and uric acid; uric acid is considered the most crucial. Although salivary antioxidants are the most effective form of protection against oxidative stress-mediated injuries, molecules also exist that disrupt the pathway of these antioxidants, thereby decreasing the effectiveness of the antioxidant defense system in the oral cavity. Molecules that seem to fulfill this antagonistic role are hydrogen peroxide when present in excess, superoxide radicals, leukotoxin secreted by an oral pathogen, and MDA. Other molecules may disrupt the antioxidant pathway, but the literature relating to this area is not vast. Research into molecules that serve as a barrier to antioxidants must be adequately conducted, as this would help in developing treatments that can protect the oral cavity, and the human body in general, from oxidative stress.

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