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Narrative Review

# Salivary Enzymes in Health and Disease

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**Abstract**

Saliva is a complex fluid produced by the salivary glands. It is the secretion of the salivary glands and constitutes one of the largest secretions of the human body. It maintains the integrity of both the soft and hard tissues of the mouth and it constitutes one of the main natural defence systems of the oral cavity. Saliva consists of varied organic and inorganic components and its secretion is influenced by sympathetic and parasympathetic stimulation. Saliva also contains hormones, antibodies, growth factors, enzymes, microbes and their products. Many of these constituents enter saliva through blood via passive diffusion, active transport or extracellular ultrafiltration. Therefore, saliva can be seen in many cases as a reflection of the physiological function of the body. It is actually a clinically informative, biological fluid (biofluid) that is useful for novel approaches to prognosis, laboratory or clinical diagnosis, and monitoring and management of patients with both oral and systemic diseases. This review article aims to elaborate and discuss about the enzymes in saliva. There are about 25 to 30 enzymes found in saliva after reviewing the literature to best of our knowledge. Newer advancements and technologies have enabled saliva to be used as a diagnostic biomarker. We also enumerated a list of enzymes present in saliva and its function as a short review for the first time in the literature here, thereby contributing our work to researchers to gain knowledge and encourage them to carry out further studies in the field of salivary enzymes.

**Keywords:** Salivary Enzymes, Saliva, Enzymes in Saliva, Health, Diseases

## Introduction

Saliva is the secretion of the salivary gland and constitutes one of the largest secretions of the human body.[1] It also contains hormones, antibodies, growth factors, enzymes, microbes and their products. Many of these constituents enter saliva through blood via passive diffusion, active transport or extracellular ultrafiltration. Therefore, saliva can be seen in many cases as a reflection of the physiological function of the body.[2] It maintains the integrity of both the soft and hard tissues of the mouth and it constitutes one of the main natural defence systems of the oral cavity. A biomarker can be defined as a biological molecule found in blood, other body fluids or tissue that is a sign of normal or abnormal process, or of a condition or disease. Saliva is a clinically informative, biological fluid (biofluid) that is useful for novel approaches to prognosis, laboratory or clinical diagnosis, and monitoring and management of patients with both oral and systemic diseases.[3]

Salivary proteome and salivary transcriptome are used as tool boxes for early detection, disease progression and therapeutic monitoring. Salivary protein and RNA'S can be used to detect oral cancer. It is easily collected and stored and ideal for early detection of disease as it contains specific soluble biological markers (biomarkers). Saliva contains multiple biomarkers which make it useful for multiplexed assays that are being developed as Point-Of-Care (POC) devices, rapid tests, or in more standardized formats for centralized clinical laboratory operations. Salivary diagnostics is a dynamic field that is being incorporated as part of disease diagnosis, clinical monitoring and for making important clinical decisions for patient care.[4]

It has been used as a diagnostic fluid in medicine. Enzymes in saliva can originate from cells in the salivary glands, microorganisms, epithelial cells, neutrophils and can be derived from gingival crevicular fluid. Numerous enzymes have been previously demonstrated in saliva. They include amylase, invertase,

maltase, carbonic anhydrase, urease, oxidases, catalase, proteolytic enzymes, lipase, phosphatases, lysozyme, and hyaluronidase.[1] Chauncy et al. had classified salivary enzymes based on their source (Table 1).

**Table 1.** Classification of Salivary Enzymes

| Enzyme | Source | | |
|---|---|---|---|
| | Glands | Microorganisms | Leucocytes |
| Carbohydrases | | | |
| Amylase | X | O | O |
| Maltase | O | X | X |
| Invertase | O | X | O |
| Beta-glucuronidase | X | X | X |
| Beta-D-galactosidase | O | X | X |
| Beta-D-glucosidase | O | X | O |
| Lysozyme | X | O | X |
| Hyaluronidase | O | X | O |
| Mucinase | O | X | O |
| Esterases | | | |
| Acid phosphatase | X | X | X |
| Alkaline phosphatase | X | X | X |
| Hexosediphosphatase | O | X | O |
| Aliesterase | X | X | X |
| Lipase | X | X | X |
| Acetylcholinesterase | X | O | X |
| Pseudo-cholinesterase | X | X | X |
| Chondrosulfatase | O | X | O |
| Arylsulfatase | O | X | O |
| Transferring enzymes | | | |
| Catalase | O | X | O |
| Peroxidase | X | O | X |
| Phenyloxidase | O | X | O |
| Succinic dehydrogenase | X | X | X |
| Hexokinase | O | X | X |
| Proteolytic enzymes | | | |
| Proteinase | O | X | X |
| Peptidase | O | X | X |
| Urease | O | X | O |
| Other enzymes | | | |
| Carbonic anhydrase | X | O | O |
| Pyrophosphatase | O | X | O |
| Aldolase | X | X | X |

There are no articles published thereafter, describing or classifying about the total number of salivary enzymes. Numerous studies have been published previously discussing about individual enzymes in varied diseased conditions. We are attempting here to compile a short review on these enzymes which have not been previously discussed in detail in any other study.

## Salivary Amylase

Salivary alpha-amylase is a calcium containing metalloenzyme that hydrolyzes the a-1, 4 linkages of starch to glucose and maltose in oral cavity. Although salivary and pancreatic amylases are similar, they are encoded by different genes (AMY1 and AMY2, respectively). In addition to starch digestion, sAA has also been shown to have an important bacterial interactive function. Various findings have demonstrated that Autonomic Nervous System (ANS) and the Sympathetic Nervous System (SNS) in particular, is involved in the release of sAA. The normal level of salivary amylase is 0-137 U/L.

In Diseases: i) Extremely overweight (obesity)- increased, ii) Alcoholic, iii) Diabetic (lower level of salivary amylase)- There was no significant correlation between salivary and blood glucose levels, iv) Psychological stress- sAA level increased significantly, V) Peptic ulcer- increased activity, Vi) Metabolic syndrome- Those who produce low levels of salivary amylase and eat high amounts of starch are at risk for developing metabolic syndrome.

### Salivary Arginase[12-14]

Arginase is one of the five key enzymes of the urea cycle, and it is found mainly in the human liver. Arginase and Nitric Oxide Synthetase (NOS) compete for a common substrate, L- arginine. Arginase uses L-arginine to produce urea and ornithine, whereas NOS uses L- arginine to produce nitric oxide. The normal level for salivary arginase is 14.45467 ± 1.68783 IU/L. It is used in assessing nutritional status in children.

In Disease: i) Argininaemia- decreased or not detected in patients with argininaemia, ii) Periodontitis- Increased, iii) Smokers- increased.

### Salivary Alkaline Phosphate[15-20]

ALP is a membrane bound enzyme, which hydrolyzes monophosphate ester bonds and increases the local concentration of phosphate ions. ALP is produced by many cells like neutrophils, fibroblasts, osteoblasts and osteoclasts which is disturbed due to diabetes, smoking, etc., pathologically. High serum levels of ALP and phosphate are associated with an increasing incidence of total mortality. Cellular Alkaline Phosphatase (ALP) is increasingly recognized as an important marker of induction of tumor cell differentiation. Rise in Salivary ALP (SALP) levels reflects inflammation and destruction of healthy tissues suggesting it as a clinical biomarker. The normal level for salivary Alkaline phosphatase is 24.70 ± 12.18 IU/L.

In Disease: Periodontitis, Smoking, Diabetes mellitus, Premalignant and malignant lesions- Increased.

### Salivary Acid Phosphatase[21-23]

ACP is the enzyme associated with bone metabolism. It is present in neutrophils and is considered as a lysosomal marker. It has been associated with bone resorption and osteoclasts activities of bones. Acid phosphatase is an indicator of increased cellular damage in the soft tissues of the periodontium and inflamed gingival tissues. The normal level for salivary acid phosphatase is 7.32 ± 4.1 IU/L.

In Disease: Periodontitis (Increased).

### Salivary Alanine Transaminase[24-28]

ALT is normally found in red blood cells, liver, heart, muscle tissue, pancreas, and kidney i.e located in the mitochondria and cytoplasm, formerly called as Serum Glutamic Oxaloacetic Transaminase (SGOT). GOT and Glutamic Pyruvate Transaminase (GPT) participate in conversion of amino acids to keto acids and therefore are required for metabolism of nitrogen and carbohydrates. Their increased activity in saliva is probably the consequence of destructive processes in the alveolar bone in advanced stages of the development of periodontal disease. The normal level for salivary Alanine transaminase is 9.95 ± 5.75 IU/L.

In Disease: Periodontitis, Smoking, Diabetes mellitus, Peptic ulcer (Increased).

### Salivary Aspartate Aminotransferase[29-32]

Formerly called glutamic oxalotransferase (GOT), an intracellular enzyme which upon cell death is released extracellularly. Aspartate aminotransferase are enzymes found mainly in the liver, but are also found in red blood cells, heart cells, muscle tissue and other organs, such as the pancreas and kidneys. It is used as a diagnostic adjunct in human cardiac and hepatic tissue necrosis, appendicitis, polymyositis, and dermatomyositis. The determination of AST levels in serum has been used for many years to identify inflammatory lesions in the heart, liver and kidney, and in cerebrospinal and synovial fluids for lesions in the brain and joints respectively. The normal level for salivary aspartate aminotransaminase is 61.33 ± 15.26 IU/ml.

In Disease: Smoking, Salivary gland disorders (Increased).

### Salivary Alanine Aminopeptidase[33]

ALAP is a proteolytic enzyme released in the periodontal tissues from leukocytes, host cells and microorganisms. It plays a key role in peptide hydrolysis and collagen degradation. The normal level for salivary alanine aminopeptidase is 5.17 ± 1.31 IU/L.

In Disease: Periodontitis: ALAP was higher in saliva of patients with chronic Periodontitis and positive correlation existed between the levels of the enzymes with the severity of Periodontitis [42.34 ± 8.96 U/L].

### Salivary Acetylcholinesterase[34- 37]

Acetylcholinesterase (AChE) is expressed not only in the Central Nervous System (CNS), Peripheral Nervous System (PNS) and muscles, but also on the surface of blood cells and saliva. AChE hydrolyzes the neurotransmitter acetylcholine (ACh). The normal level for salivary AChE is 22.7 +/- 17.4 U/L.

In Disease: Parkinson's disease, Sjogren's disease, Alzhiemier's disease, Organophosphate poisoning (Increased).

### Salivary Aldolase[38,39]

The activity of salivary aldolase was considered to be of bacterial and yeast origin. The enzyme cleaves 1 mole of fructose-1,6-diphosphate (HDP) into 1 mole each of glyceraldehyde-3-phosphate (G-3-P) and di-hydroxyacetone phosphate (DHA-P). The normal level of salivary aldolase is 26.05 ± 20.32 U/ml. In Disease: Candidiasis, Dental caries (Increased).

### Salivary Antioxidants[40- 46]

Two types of antioxidants exist in the body and saliva: enzymatic antioxidants such as catalase, superoxide dismutase, peroxidase, and glutathione peroxidase and nonenzymatic antioxidants or diet supplements and small molecules such as vitamin C, vitamin E, and uric acid. Unstimulated whole saliva has a higher con-centration of antioxidants than stimulated individual salivary gland secretions. The salivary anti-oxidants are:

1. Catalase (CAT), 2. Superoxide dismutase (Cu/Zn SOD), 3. Peroxidase (POx), and 4. Glutathione peroxidase (GSH-Px).

### Salivary Catalase

Catalase is a haemoprotein with four groups of peroxidase activities. Catalase was absent from the glandular secretions in a large series of determinations and its origin in normal saliva is presumed to be bacterial. The normal level of salivary catalase is 283.7 ± 229.7 KU/I.

In Disease: The mutagenic and cytotoxic effects of cigarette smoke might be attributed to the synthesis of free radicals and inhibition of catalase leading to decreased levels in smokers.

### Salivary Peroxidase

The source of peroxidase in saliva is predominantly glandular and a smaller amount of activity is contributed by the leukocytes. Salivary peroxidase is by far the most important antioxidant enzyme in saliva. The normal level of salivary peroxidase is 3.32 U/g.

### Salivary Glutathione Peroxidase

Glutathione peroxidase, is an extracellular antioxidant, mainly produced in the kidney and has been found in numerous human fluids. Glutathione peroxidase is a selenium containing enzyme which detoxifies hydrogen peroxide and various hydroperoxides with glutathione as a reducing agent; their main biologic role is to protect the organism against oxidative injuries. The normal salivary level of GPx is 2.61 ± 2.71 (nmol/min/ml). Its level is increased in non-smokers and decreased in apthaous stomatitis.

### Salivary Superoxide Dismutase

Superoxide Dismutase (SOD) enzyme is responsible for preventing the effect of oxidative agents within the cells and cellular organelles, such as mitochondria and peroxisomes. SOD plays a critical role in the reduction of lipid and hydrogen peroxides. It is actually one of the antioxidant enzymes that protects the cell against the deleterious effects of ROS. The normal level of salivary superoxide dismutase is 4.73 ± 3.36 U/ml.

In Disease: Increase- Diabetes mellitus, smoking; Decreased- Oral Premalignant and malignant lesions.

### Salivary Beta Galactosidase[47,48]

β-Galactosidase is mainly produced by Gram positive bacteria in the outer layers of the biofilm. Glycosylated proteins are initially deglycosylated by *β*-galactosidase produced by Gram-positive bacteria before being digested by periodontopathic bacteria. The activity of β-galactosidase in saliva may be mainly responsible for the malodor production in physiological halitosis.

### Salivary Beta Glucouronidase[49,50]

Beta Glucuronidase is a PMN derived lysosomal acid hydrolase, which is stored in primary azurophil granules and it contributes to non-collagenous matrix degradation. The β Glucuronidase together with hyaluronidase is involved in the catabolism of proteoglycans. The normal value of salivary β- glucuronidase is 639.06 ± 1.19 U/L. In Disease: Increased in periodontitis, diabetes mellitus, pre-conception.

### Salivary Carbonic Anyhydrase[51-54]

CA VI is a secretory iso-enzyme in saliva which plays a role in pH regulation, carbon dioxide and bicarbonate transport, maintenance of water and electrolyte balance and anticaries activity. The normal level of salivary carbonic anyhydrase is 0.18 -0.11 IU/L.

In Disease: Increased in dental caries.

### Salivary Cathepsin[55-57]

Cathepsins are specific mannose-6-P-rich carbohydrates lysosomal cysteine proteases which may release into

the extracellular milieu in precursor and/or active forms. Cathepsin L is produced by salivary gland and released into oral fluids. Cathepsin L can be produced in human gingival fibroblasts, and its production can be enhanced under the influence of interleukin-6, implicating inflammatory processes. However, its level remains unchanged in CHD.

### Salivary Chitinase[58-60]

Chitin is a polymer of the monosaccharide N-acetyl-glucosamine, and is present in plants and lower organisms. Human salivary chitinase could play a role in the defence against chitin-containing oral pathogens such as Candida albicans, A. fumigatus and Cryptococcus neoformans. The normal salivary chitinase level is of 230 mU/ml.

In Disease: Increased in Sjogren's syndrome, candidiasis, Periodontitis.

### Salivary Dipeptidylpeptidase[61-64]

Dipeptidyl peptidase is a transmembrane glycoprotein and exoprotease that cleaves N-terminal dipeptides from various substrates playing a key role in modification, processing, and/or inactivation of peptides, such as peptide hormones, various chemokines, neuro- peptides, and growth factors. DPP4/CD26 was originally characterized as a T cell differentiation antigen and is expressed on various cell types. DPP-IV is a strong inhibitor of the antilipolytic activity of neuropeptide Y, which is one of the best peptide substrates of the enzyme. DPP IV is a peptidyl peptidase which seems to be involved in collagen degradation. The normal value of salivary dipeptidylpeptidase is 8.77+/- 1.3779 IU/L.

In Disease: Increased in obesity, Diabetes, Oral squamous cell carcinoma, Periodontitis.

### Salivary Elastase[66,67]

Elastase is a neutral serine proteinase (endopeptidase) "stored" in azurophilic granules of granulocytes, capable of degrading a large spectrum of various molecules in human tissues, including periodontal tissues, such as collagen, laminin, fibronectin, proteo- glycans and elastin.

The normal laboratory value for salivary elastase is 2849.38 ng/ml.

In Disease: Increased in Periodontitis.

### Salivary Hyaluronidase[67,68]

Hyaluronidases are a group of mucolytic enzymes which hydrolyse hyaluronic acid. These substances are present in the gingival tissues, the dental pulp, dentin, and blood vessels. Some bacteria have capsules composed of hyaluronic acid.

In Disease: Initiator and spreader of dental caries.

### Salivary Lactate Dehydrogenase[69-74]

LDH is an enzyme detectable in the cytoplasm of almost every cell in the human body and becomes extracellular upon cell death. The activity of isoenzymes profile of LDH is different in saliva and in the plasma. LDH4 and LDH5 enzymes dominate in saliva, whereas LDH1 and LDH2 dominate in the blood. Oral epithelial cells are considered the major source. Its main function is to catalyze the oxidation of lactate to pyruvate. The normal level of salivary LDH is 90.1 +/-28.8 U/L.

In Disease: Increased in hypoxia, fibrosis, diabetes, periodontitis, oral premalignant and malignant lesions.

### Salivary Lipase[75,76]

Lingual lipase is important for infant nutrition. Lingual lipase also reportedly contributes to the digestion of lipids in adults along with gastric lipase. The normal level for salivary lipase is 40.9 ± 1.7 U/L which is increased in obese patients.

### Salivary Lysozyme[77-80]

Salivary lysozyme is locally produced in the oral cavity, and is derived from neutrophils in response to oral infection. Lysozyme is an important component of antibacterial in saliva. It also plays a key role in antiviral properties and induces lysis of tumour cells. Thus, the raised concentration of lysozyme in cancer patients may be explained by the antitumor effect of lysozyme. The normal level of salivary lysozyme is 51.64+/-2.82 ng/ml.

In Disease: Increased in diabetes, cardiovascular patients, leukemia, oral infections.

### Salivary Matrix Metalloproteinase[81-84]

Humans have 24 matrix in genes including duplicated MMP-23 genes. Matrix Metalloproteinases (MMP) are calcium- dependent zinc containing endopeptidases that play an important role in normal physiological processes such as tissue development and remodelling as well as in pathological processes. The main function of matrixin has been considered to be the degradation

and removal of ECM molecules from the tissue. It is controlled by inflammatory cytokines, growth factors, hormones, cell–cell and cell–matrix interaction. The normal level of salivary matrix metalloproteinase is 674.8 (188.4–1,144) ng/ml.

In Disease: Increased in periodontitis, smokers, oral premalignant and malignant lesions.

### Salivary Myeloperoxidase[85-88]

MPO is released from azurophilic granules of polymorphonuclear cells or neutrophils to catalyze the formation of bactericidal compounds such as hypochlorous acid (HOCl). MPO is often used as an inflammatory marker for early detection of several diseases including urinary tract infection, ischemic heart disease and acute coronary heart syndrome and cardiovascular risk in pre pubertal obese children and in patients with type 2 diabetes. The normal level of salivary myeloperoxidase is 0.485 ± 0.267 mg/ml.

In Disease: Gingivitis, Periodontitis.

### Salivary Neuraminidase[89]

The oral bacteria would seem to be the prime source of salivary neuraminidase. T is derived from cells such as leukocytes or epithelial cells in the oral cavity. The normal level of salivary neuraminidase is 4.7 mg/ml, increased in Periodontitis.

### Salivary Pseudocholinesterase[90]

PCE activity in whole saliva is derived from salivary glands, micro-organisms, leucocytes, and GCF, rather than directly from plasma. The normal level of PCE in saliva is 12.7+/- 0.8 U/L. Its level is mainly increased in periodontitis in saliva.

## Conclusion

Salivary tests will pave the way for chair-side diagnosis of multiple oral and systemic diseases at dental offices. However, much work needs to be done to incorporate saliva-based diagnostics into daily use. Salivary collection methods and biomarkers need to be standardized and validated. It is expected that the advent of sensitive and specific salivary diagnostic tools and the establishment of defined guidelines will make salivary diagnostics a reality in the near future. In conclusion, saliva is a biological fluid that offers several opportunities in diagnosis, toxicology and in forensic science. Furthermore, many salivary proteins offer great potential in clinical and epidemiological research, in oral as well as in general health studies.

## Conflict of Interest

The authors declare no conflicts of interest.

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