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# Salivary Biomarkers in Diagnosis of Dental caries - A Review Article

Review Article

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## Abstract

Saliva can be used to study the physiological state of the body, having the potential to be used in early detection and diagnosis of diseases. Saliva is secreted from the salivary glands and has multiple functions, including oral cavity cleaning and protection, antibacterial effects and digestion. With the rapid advancement in salivaomics, saliva is well recognized as a pool of biological markers. Saliva contains various microbes and host biological components that could be used for caries risk assessment. The determination of biomarkers in saliva is becoming an important part of laboratory diagnostics and the prediction of dental caries. Biomarkers in saliva (e.g., enzymes, protein markers, or oxidative stress markers) can be used for activity determination for dental caries prognosis. Saliva is an interesting alternative diagnostic body fluid with several specific advantages over blood. These include non-invasive and easy collection and related possibility to do repeated sampling. This makes saliva very interesting for clinical biochemistry of oral diseases. This review summarizes the latest advancements in saliva-related studies and addresses the potential salivary biomarkers in the early diagnosis of dental caries.

**Keywords:** Biomarkers; Diagnosis; Dental Caries; Genetic; Salivary Proteins.

## Introduction

Biomarker is an objectively measured and evaluated indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to therapeutic intervention. They are entities within the body capable of providing impartial information regarding the current physiologic state of a living organism [1]. Biomarkers exist in a variety of different forms, including antibodies, microbes, DNA, RNA, lipids, metabolites, and proteins. Alterations in their concentration, structure, function, or action can be associated with the onset, progression, or even regression of a particular disorder.

## Salivary Biomarkers

The oral cavity is a diverse habitat composed of teeth, gingival sulci, the tongue, hard and soft palates, the buccal mucosa, and tonsils. Each structure is colonized by bacteria and continuously bathed in saliva. Saliva can be used to study the physiological state of body, having the potential to be used in early detection and diagnosis of diseases [2]. There is an association between elevated caries prevalence and/or incidence among people with a pathologically low saliva flow rate, compromised buffering capacity and early colonization or high titer of mutans streptococci in saliva. Studies have shown that salivary bacteria, may also be a used as an indicator of dental caries [3]. There are associations between dental caries and other saliva parameters, such as other cariogenic species (Lactobacillus spp., Streptococcus sanguis group, Streptococcus salivarius, Actinomyces spp. and Candida albicans), diversity of salivary microbiomes, inorganic and organic constituents (electrolytes, immunoglobulins, other proteins and peptides) and some functional properties [4](sugar clearance rate, etc).

## Sample Collection

The usual salivary collection methods include a draining method using a Proflow Sialometer, a spitting method, a suction method, swab or absorbent methods and the use of salivette. The physi-

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ological pH of saliva ranges from 6.2 to 7.4. Chewing paraffin wax is the most commonly employed saliva stimulating method. The samples are usually collected on ice or any container. The collected samples are immediately centrifuged at 13000 rpm for 5 minutes to remove the insoluble material, and all the procedures are performed at 40 C. The supernatant is removed and placed in Eppendorf tubes that are stored at -800°C [5].

There are many processing units for testing saliva. Most common method performed for testing are enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR), high resolution mass spectrometry (HRMS), Western blotting technique, newer technology such as fibre-optic-based-detection [6]. The salivary buffer capacity can be measured by Dentobuff method. The saliva Total antioxidant capacity (TAC) measurement can be performed using spectrophotometry by adaptation of 2, 2'-azino-di-(3-ethylbenzthiazoline-6-sulphonate) ABTS assay [7]. Major drawback of ELISA is that it requires more invasive method for collection of samples and trained personnel [8].

## Various Salivary Biomarkers

The abundant protein content present in the saliva acts as biomarkers. The various salivary proteins that can be used as biomarkers for dental caries are soluble immunoglobulin A, mucin 1 and 2, cystain S, statherins, defensins, CD14 and glycosyltransferase. These act as potential markers for dental caries.

### Soluble immunoglobulin

Salivary antibodies are the first line defence against antigens present in saliva, epithelial and tooth surface. Salivary immunoglobulins are produced by plasma cells present in stroma of salivary glands, adjacent to salivary ducts and oral mucosa. The main salivary immunoglobulin of whole saliva is secretary immunoglobulin A (sIgA), is constitutively secreted into saliva. It has the ability to inhibit bacterial adhesion to the epithelial cells, and is considered as the first line of defence against bacterial invasion [9]. It acts synergistically with other defence mechanisms, such as the lactoferrins, perioxidase, agglutinins and mucins.

The normal level of sIgA in individuals ranges from 4-30mg/dL. This level is changed by numerous conditions, like malnutrition, obesity, infections, stress, smoking, salivary flow rate, hormonal factors. In elderly persons, a decreased level of sIgA is associated with an increase in root caries and candidiasis.

Based on a study on an Indian population [10], it was observed that the total salivary concentration of sIgA was higher in caries free children than in other groups with active caries. Similarly Omar et al demonstrated that the sIgA levels decreased with the increase of the carious lesions [11]. The group with lower caries experience has a higher level of sIgA than those caries free group. In overview, the levels of sIgA appeared to be inversely proportional to DMFT. Contrary to this, Vitorino et al [12] reported that the IgA was present at higher concentration in caries susceptible group.

All these studies revealed different correlation between the salivary IgA levels and caries. The first two studies found a negative correlation while the last study had a positive correlation, which associated with higher levels of IgA with higher caries susceptibility.

### Mucins 1 and 2

Mucins are glycoproteins produced by submandibular, sublingual, labial and palatinal minor salivary glands. They have an important role in concentrations of other antimicrobial proteins in oral mucosa such as lysozymes, IgA and cystatin. Saliva contains two forms of mucins, the high-molecular-weight mucin glycoprotein-1(MG1 or MUC5b) and the low-molecular-weight glycoprotein-2(MG2 or MUC7). These mucins control the process of demineralisation and remineralisation.

In a study on Mexican population, a correlation between the quantity of proteins MG1 and MG2 and DMFT index was observed, where the absence of 6-13% of these mucins was associated with higher DMFT index [13].

### Cystatin S and Statherin

Saliva presents seven different cystatins, cystatin A, cystatin B, cystatin C, cystatin D, cystatin S, cystatin SA and cystatin SN[14]. Cystatin S (AA1-8) variant, is a truncated form of cystatin S formed by proteases on the carboxyl side of arginine. Cystatin S can be phosphorylated in five sites. These phosphorlated forms have important function in the regulation of calcium level and in pellicle formation.

Literature search showed that the saliva from caries free group had a higher concentration of Cystatin S, SN1, SN2 and SA-III. The study reported that DMFT had a negative correlation with Salivary Cystatin.[12]

Statherin is a protein with the most important function being the inhibition of precipitation in saturated solutions of calcium. It is the primary regulator of mineralisation in the oral cavity. The salivary levels of statherin and variant cystatin S (AA1-8) have an inverse correlation with occlusal caries [15]. Higher levels of statherin and cystatin S were observed in caries-free individuals. Research report reveals correlation between Cystatin S and Statherin, and bacterial aggregation and adherence. Rudney et al [16] investigated the influence of bacterial aggregation, adherence and killing on the risk of dental caries. The results demonstrated the reduction of caries in groups with high aggregation –adherence. These groups had higher levels of cystatin S and statherin.

### Glucosyltranferase B

Bacteria-derived glucosyltransferases (Gtf) (EC 2.4.1.5), through synthesizing glucan polymers from sucrose and starch hydrolysates, play an essential role in the etiology and pathogenesis of caries. Vacca Smith et al [17] evaluated the salivary glucosyltransferase B as a possible marker for caries activity. They reported that there was a positive relation between mutans streptococci populations in saliva and caries activity. They concluded that GtfB levels in saliva correlate strongly with presence of clinical caries and with number of carious lesions in young children.

### Superoxide Dismutase

Hedge et al [18] evaluated the biochemical indicators of dental

caries in saliva with the use of superoxide dismutase (SOD) activity, copper and zinc. They reported that SOD activity as well as copper and zinc levels increased in the caries-active group and showed statistically significant results.

**Carbonic anhydrase enzyme**

Picco et al [19] evaluated thatchildren with a higher activity of carbonic anhydrase (CA) VI in saliva are more likely to develop dental caries. They reported that the salivary CA VI activity was higher in children with caries.They found a negative correlation between buffering capacity and dental caries. Also, in the caries group they found a positive correlation between the concentration and the activity of CA VI and a negative correlation between BC and CA VI activity. A high activity of CA and a low salivary flow rate were associated with dental caries.

**Total antioxidant capacity (TAC)**

Mahjoud et al [20] evaluated thecomparison of TAC in saliva of children with severe early childhood caries and caries-free children. They compared the TAC levels in the unstimulated whole saliva of children with severe early childhood caries (S-ECC) and caries-free children and concluded that TAC levels and salivary total protein increased in children with S-ECC compared with caries-free children.

**Magnetic-bead salivary peptidome**

Si et al [21] in their study on magnetic bead-based salivary peptidome profiling analysis for severe early childhood caries proposed a new strategy for screening high-risk populations. Based on a novel method, the salivary protein profiling can be done. They used matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) combined with weak cation exchange magnetic beads, and peptide mass fingerprints were created by scanning mass spectrometry signals.

**Salivary peroxidase**

Lamberts et al [22] evaluated thecomparison of salivary peroxidase system components in caries-free and caries-active naval recruit. Based on a single point measurement of saliva no significant correlation between caries incidence and concentrations of salivary peroxidase system was observed. However generation of hypothiocyanite in saliva was associated with a decrease in enzyme activity. There are reports revealing association between smoking and hypothiocyanite. Smokers had significantly elevated thiocyanate and hypothiocyanite compared to nonsmokers. When the salivary peroxidase system is activated, additional supplements of thiocyanate produce increased generation of hypothiocyanite.

**Matrix Metalloproteinase (MMP)**

Tannura et al [23] evatuated the relation between MMP polymorphisms and dental caries. Matrix metalloproteinases (MMPs) and their tissue inhibitors have been suggested to be involved in the caries process. The MMPs under research are MMP2 (rs243865), MMP9 (rs17576), MMP13 (rs2252070), and TIMP2 (rs7501477) whether they are associated with caries. Genetic variation in MMP13 may contribute to individual difference in caries susceptibility. However allelic and genotype frequencies of the polymorphisms in MMP9 were similar in caries affected and caries free individuals.

**Nitric oxide (NO) concentration**

Bayindir et al [24] evaluated thenitric oxide concentrations in saliva and dental plaque in relation to caries experience and oral hygiene. The result showed that the patients with high DMFT had significantly higher NO concentrations in saliva and plaque than those with low DMFT. Plaque NO concentrations were significantly higher than in saliva. NO production might be a host defence mechanism when dental caries increases or oral hygiene deteriorates.

## Genetic

The saliva characteristics are controlled by many factors, including genetic factors. The genetic mechanisms in the aetiology of caries encompass, 4 main groups of genes responsible for (1) the development of enamel, (2) formation and composition of saliva, (3) immunological responses, and (4) carbohydrate metabolism. BMP7, ALOX15, AQP5, TUFT1, KRT75 genes in tooth formation were found to be associated with increased caries susceptibility and a risk factor for caries [25-29]. Hallotype ACA and GG are associated with high caries susceptibility [30, 31]. These are the genes that are associated with the compositon and functions of saliva. DEFB1 and MBL2 are the genes influencing immune response and are found to have a high caries intensity [32, 33]. TAS1R2 and GLUT2 are the genes influencing carbohydrate metabolism and are found to have higher caries intensity [34, 35].

Küchler et al [36] reported that thegenes involved in the enamel development are associated with calcium and phosphorus level in saliva. They reported that there were genetic variations in AMELX, AMNB and ESRRB which were associated with the calcium level in saliva and a borderline association was observed in ENAM allele distribution shown with phosphate level in saliva. The antimicrobial peptides human β-defensins (hBDs) are encoded by β-defensin genes (DEFBs) and are possibly involved in caries susceptibility. Lips et al [37] in their study concluded that genetic polymorphism in miRNA202 is involved in hBD1 salivary level as well as caries experience in children.

Gene variants affecting taste preference and glucose transport were recently associated with caries risk. Many clinical studies showed that the difference in sensitivity to the bitter taste of 6-n-propylthiouracil (PR7OP) is a heritable trait and may influence children's caries development. Oter et al [38] in their study evaluated the relation between 6-n-propylthiouracil sensitivity and caries activity in school children. The results concluded that PROP non-tasters were significantly more likely to have high caries risk than PROP tasters. Izakovicova Holla et analyzed two common polymorphisms in the sweet taste receptor (TAS1R2) and glucose transporter (GLUT2) genes in children with dental caries and healthy controls among the Czech population. They identified that GLUT2 and TASR1 polymorphisms influenced the risk of caries.[39, 40]

Our team has numerous highly cited publications on well-designed clinical trials and lab studies on various topics in the past couple of years [41-55]. Our institution is passionate about high

quality evidence based research and has excelled in various fields [56-65]. The current topic was reviewed with an intention to explore the diagnostic tool to be put into research and practice.

## Conclusion

Saliva has been analysed for diagnostic purposes. Salivary biomarkers are useful in the diagnosis of variety of diseases. It is non invasive, uncomplicated, diagnostic tool. Dental caries that can be monitored by assaying salivary biomarkers opens a wider view. The dental caries affect the salivary proteome. Consequently saliva appears to be a potential source of biomarkers for dental caries. Based on the analysis of several studies, there are various protein candidate, salivary enzymes, genes which play the role of biomarker for dental caries. More studies on salivary biomarkers may prove greater insight in to various other diseases in human population.

## References


[1]. Silberring J, Ciborowski P. Biomarker discovery and clinical proteomics. Trends Anal. Chem. 2010 Feb 1;29(2):128-40.

[2]. Ilyin SE, Belkowski SM, Plata-Salamán CR. Biomarker discovery and validation: technologies and integrative approaches. Trends Biotechnol. 2004 Aug 1;22(8):411-6.

[3]. Kurian S, Grigoryev Y, Head S, Campbell D, Mondala T, Salomon DR. Applying genomics to organ transplantation medicine in both discovery and validation of biomarkers. Int. Immunopharmacol. 2007 Dec 20;7(14):1948-60.

[4]. Segata N, Haake SK, Mannon P, Lemon KP, Waldron L, Gevers D, et al. Composition of the adult digestive tract bacterial microbiome based on seven mouth surfaces, tonsils, throat and stool samples. Genome Biol. 2012 Jun 14;13(6):42.Pubmed PMID: 22698087.

[5]. Rahim ZH. Saliva in research and clinical diagnosis an overview. Annals Dent Univ Malaya. 1998 Dec 31;5(1):11-6.

[6]. Navazesh M, Christensen CM. A comparison of whole mouth resting and stimulated salivary measurement procedures. J Dent Res. 1982 Oct;61(10):1158-62.

[7]. Frostell G. A colorimetric screening test for evaluation of buffer capacity of saliva. Swed Dent.1980; J4:81-86.

[8]. Gomes-Keller MA, Gönczi E, Tandon R, Riondato F, Hofmann-Lehmann R, Meli ML, et al. Detection of feline leukemia virus RNA in saliva from naturally infected cats and correlation of PCR results with those of current diagnostic methods. J Clin Microbiol. 2006 Mar;44(3):916-22.Pubmed PMID: 16517876.

[9]. Marcotte H, Lavoie MC. Oral microbial ecology and the role of salivary immunoglobulin A. Microbiol Mol Biol Rev. 1998 Mar 1;62(1):71-109.

[10]. Chawda JG, Chaduvula N, Patel HR, Jain SS, Lala AK. Salivary SIgA and dental caries activity. Indian Pediatr. 2011 Sep;48(9):719-21.

[11]. Omar OM, Khattab NM, Rashed LA. Glucosyltransferase B, immunoglobulin a, and caries experience among a group of Egyptian preschool children. J Dent Child (Chic). 2012 May-Aug;79(2):63-8.Pubmed PMID: 22828760.

[12]. Vitorino R, de Morais Guedes S, Ferreira R, Lobo MJ, Duarte J, Ferrer-Correia AJ, et al. Two-dimensional electrophoresis study of in vitro pellicle formation and dental caries susceptibility. Eur J Oral Sci. 2006 Apr;114(2):147-53.Pubmed PMID: 16630307.

[13]. Banderas-Tarabay JA, Zacarías-D'Oleire IG, Garduño-Estrada R, Aceves-Luna E, González-Begné M. Electrophoretic analysis of whole saliva and prevalence of dental caries. A study in Mexican dental students. Arch Med Res. 2002 Sep-Oct;33(5):499-505.Pubmed PMID: 12459324.

[14]. Vitorino R, Lobo MJ, Ferrer-Correira AJ, Dubin JR, Tomer KB, Domingues PM, et al. Identification of human whole saliva protein components using proteomics. Proteomics. 2004 Apr;4(4):1109-15.

[15]. Fábián TK, Hermann P, Beck A, Fejérdy P, Fábián G. Salivary defense proteins: their network and role in innate and acquired oral immunity. Int J Mol Sci. 2012;13(4):4295-320.Pubmed PMID: 22605979.

[16]. Rudney JD, Staikov RK, Johnson JD. Potential biomarkers of human salivary function: a modified proteomic approach. Arch Oral Biol. 2009 Jan;54(1):91-100.Pubmed PMID: 18804197.

[17]. Vacca Smith AM, Scott-Anne KM, Whelehan MT, Berkowitz RJ, Feng C, Bowen WH. Salivary glucosyltransferase B as a possible marker for caries activity. Caries Res. 2007;41(6):445-50.Pubmed PMID: 17827962.

[18]. Hegde MN, Hegde ND, Ashok A, Shetty S. Biochemical indicators of dental caries in saliva: an in vivo study. Caries Res. 2014;48(2):170-3.Pubmed PMID: 24504381.

[19]. Picco DD, Lopes LM, Marques MR, Line SR, Parisotto TM, Dos Santos MN. Children with a higher activity of carbonic anhydrase VI in saliva are more likely to develop dental caries. Caries Res. 2017;51(4):394-401.

[20]. Mahjoub S, Ghasempour M, Gharage A, Bijani A, Masrourroudsari J. Comparison of total antioxidant capacity in saliva of children with severe early childhood caries and caries-free children. Caries Res. 2014;48(4):271-5.

[21]. Si Y, Ao S, Wang W, Chen F, Zheng S. Magnetic bead-based salivary peptidome profiling analysis for severe early childhood caries. Caries Res. 2015;49(1):63-9.Pubmed PMID: 25547533.

[22]. Lamberts BL, Pruitt KM, Pederson ED, Golding MP. Comparison of salivary peroxidase system components in caries-free and caries-active naval recruits. Caries Res. 1984;18(6):488-94.Pubmed PMID: 6091882.

[23]. TannurePN, KüchlerEC, Falagan-Lotsch P, Amorim LMF, Raggio Luiz R, et al. MMP13 polymorphism decreases risk for dental caries. Caries Res.2012;46:401–407.

[24]. Bayindir YZ, Polat MF, Seven N. Nitric oxide concentrations in saliva and dental plaque in relation to caries experience and oral hygiene. Caries Res. 2005 Mar-Apr;39(2):130-3.Pubmed PMID: 15741725.

[25]. https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Early+childhood+caries+is+associated+with+genetic+variants+in+enamel+formation+and+immune+response+genes&btnG=.

[26]. Anjomshoaa I, Briseño-Ruiz J, Deeley K, Poletta FA, Mereb JC, Leite AL, et al. Aquaporin 5 Interacts with Fluoride and Possibly Protects against Caries. PLoS One. 2015 Dec 2;10(12):e0143068.Pubmed PMID: 26630491.

[27]. Duverger O, Ohara T, Shaffer JR, Donahue D, Zerfas P, Dullnig A, et al. Hair keratin mutations in tooth enamel increase dental decay risk. J Clin Invest. 2014 Dec 1;124(12):5219-24.

[28]. Morrison J, Laurie CC, Marazita ML, Sanders AE, Offenbacher S, Salazar CR, et al. Genome-wide association study of dental caries in the Hispanic Communities Health Study/Study of Latinos (HCHS/SOL). Hum Mol Genet. 2016 Feb 15;25(4):807-16.

[29]. Shaffer JR, Carlson JC, Stanley BO, Feingold E, Cooper M, Vanyukov MM, et al. Effects of enamel matrix genes on dental caries are moderated by fluoride exposures. Hum Genet. 2015 Feb;134(2):159-67.Pubmed PMID: 25373699.

[30]. Wang X, Shaffer JR, Zeng Z, Begum F, Vieira AR, Noel J, et al. Genome-wide association scan of dental caries in the permanent dentition. BMC oral health. 2012 Dec;12(1):57.

[31]. Li ZQ, Hu XP, Zhou JY, Xie XD, Zhang JM. Genetic polymorphisms in the carbonic anhydrase VI gene and dental caries susceptibility. Genet Mol Res. 2015 Jun 1;14(2):5986-93.

[32]. Olszowski T, Adler G, Janiszewska-Olszowska J, Safranow K, Kaczmarczyk M. MBL2, MASP2, AMELX, and ENAM gene polymorphisms and dental caries in Polish children. Oral Dis. 2012 May;18(4):389-95.Pubmed PMID: 22221294.

[33]. Krasone K, Lāce B, Akota I, Care R, Deeley K, Küchler EC, et al. Genetic variation in the promoter region of beta-defensin 1 (DEFB 1) is associated with high caries experience in children born with cleft lip and palate. Acta Odontol Scand. 2014 Apr;72(3):235-40.Pubmed PMID: 23964634.

[34]. Haznedaroğlu E, Koldemir-Gündüz M, Bakır-Coşkun N, Bozkuş HM, Çağatay P, Süsleyici-Duman B, et al. Association of sweet taste receptor gene polymorphisms with dental caries experience in school children. Caries Res. 2015;49(3):275-81.Pubmed PMID: 25924601.

[35]. Robino A, Bevilacqua L, Pirastu N, Situlin R, Di Lenarda R, Gasparini P, et al. Polymorphisms in sweet taste genes (TAS1R2 and GLUT2), sweet liking, and dental caries prevalence in an adult Italian population. Genes Nutr. 2015 Sep;10(5):485.Pubmed PMID: 26268603.

[36]. Küchler EC, Pecharki GD, Castro ML, Ramos J, Barbosa F Jr, Brancher JA, et al. Genes Involved in the Enamel Development Are Associated with Calcium and Phosphorus Level in Saliva. Caries Res. 2017;51(3):225-230. Pubmed PMID: 28395292.

[37]. Lips A, Antunes LS, Antunes LA, Abreu JGB, Barreiros D, Oliveira DSB, et al. Genetic Polymorphisms in DEFB1 and miRNA202 Are Involved in Salivary Human β-Defensin 1 Levels and Caries Experience in Children. Caries Res. 2017;51(3):209-215.Pubmed PMID: 28343232.

[38]. Öter B, Ulukapı I, Ulukapı H, Topçuoğlu N, Cıldır S. The relation between 6-n-propylthiouracil sensitivity and caries activity in schoolchildren. Caries Res. 2011;45(6):556-60.Pubmed PMID: 22041784.

[39]. Holla LI, Linhartova PB, Lucanova S, Kastovsky J, Musilova K, Bartosova M, et al. GLUT2 and TAS1R2 polymorphisms and susceptibility to dental caries. CariesRes. 2015;49(4):417-24.

[40]. Haznedaroğlu E, Koldemir-Gündüz M, Bakır-Coşkun N, Bozkuş HM, Çağatay P, Süsleyici-Duman B, et al. Association of sweet taste receptor gene

polymorphisms with dental caries experience in school children. Caries Res. 2015;49(3):275-81.Pubmed PMID: 25924601.
[41]. Govindaraju L, Gurunathan D. Effectiveness of Chewable Tooth Brush in Children-A Prospective Clinical Study. J Clin Diagn Res. 2017 Mar;11(3):ZC31-ZC34.Pubmed PMID: 28511505.
[42]. Christabel A, Anantanarayanan P, Subash P, Soh CL, Ramanathan M, Muthusekhar MR, et al. Comparison of pterygomaxillary dysjunction with tuberosity separation in isolated Le Fort I osteotomies: a prospective, multi-centre, triple-blind, randomized controlled trial. Int J Oral Maxillofac Surg. 2016 Feb;45(2):180-5.Pubmed PMID: 26338075.
[43]. Soh CL, Narayanan V. Quality of life assessment in patients with dentofacial deformity undergoing orthognathic surgery--a systematic review. Int J Oral Maxillofac Surg. 2013 Aug;42(8):974-80.Pubmed PMID: 23702370.
[44]. Mehta M, Deeksha, Tewari D, Gupta G, Awasthi R, Singh H, et al. Oligonucleotide therapy: An emerging focus area for drug delivery in chronic inflammatory respiratory diseases. Chem Biol Interact. 2019 Aug 1;308:206-215.Pubmed PMID: 31136735.
[45]. Ezhilarasan D, Apoorva VS, Ashok Vardhan N. Syzygium cumini extract induced reactive oxygen species-mediated apoptosis in human oral squamous carcinoma cells. J Oral Pathol Med. 2019 Feb;48(2):115-21.
[46]. Campeau PM, Kasperaviciute D, Lu JT, Burrage LC, Kim C, Hori M, et al. The genetic basis of DOORS syndrome: an exome-sequencing study. Lancet Neurol. 2014 Jan;13(1):44-58.Pubmed PMID: 24291220.
[47]. Sneha S. Knowledge and awareness regarding antibiotic prophylaxis for infective endocarditis among undergraduate dental students. Asian J Pharm Clin Res. 2016 Oct 1:154-9.
[48]. Christabel SL, Linda Christabel S. Prevalence of type of frenal attachment and morphology of frenum in children, Chennai, Tamil Nadu. World J Dent. 2015 Oct;6(4):203-7.
[49]. Kumar S, Rahman R. Knowledge, awareness, and practices regarding biomedical waste management among undergraduate dental students. Asian J Pharm Clin Res. 2017;10(8):341.
[50]. Sridharan G, Ramani P, Patankar S. Serum metabolomics in oral leukoplakia and oral squamous cell carcinoma. J Cancer Res Ther. 2017 Jul 1;13(3):556-61.
[51]. Ramesh A, Varghese SS, Doraiswamy JN, Malaiappan S. Herbs as an antioxidant arsenal for periodontal diseases. J Intercult Ethnopharmacol. 2016 Jan 27;5(1):92-6.Pubmed PMID: 27069730.
[52]. Thamaraiselvan M, Elavarasu S, Thangakumaran S, Gadagi JS, Arthie T. Comparative clinical evaluation of coronally advanced flap with or without platelet rich fibrin membrane in the treatment of isolated gingival recession. J Indian Soc Periodontol. 2015 Jan;19(1):66-71.
[53]. Thangaraj SV, Shyamsundar V, Krishnamurthy A, Ramani P, Ganesan K, Muthuswami M, et al. Molecular Portrait of Oral Tongue Squamous Cell Carcinoma Shown by Integrative Meta-Analysis of Expression Profiles with Validations. PLoS One. 2016 Jun 9;11(6):e0156582.Pubmed PMID: 27280700.
[54]. Ponnulakshmi R, Shyamaladevi B, Vijayalakshmi P, Selvaraj J. In silico and in vivo analysis to identify the antidiabetic activity of beta sitosterol in adipose tissue of high fat diet and sucrose induced type-2 diabetic experimental rats. Toxicol Mech Methods. 2019 May;29(4):276-290.Pubmed PMID: 30461321.
[55]. Ramakrishnan M, Shukri M. Fluoride, Fluoridated Toothpaste Efficacy And Its Safety In Children-Review. Int. J. Pharm. Sci. Res. 2018 Oct 1;10(04):109-14.
[56]. Vijayashree Priyadharsini J. In silico validation of the non-antibiotic drugs acetaminophen and ibuprofen as antibacterial agents against red complex pathogens. J Periodontol. 2019 Dec;90(12):1441-1448.Pubmed PMID: 31257588.
[57]. Pc J, Marimuthu T, Devadoss P, Kumar SM. Prevalence and measurement of anterior loop of the mandibular canal using CBCT: A cross sectional study. Clin Implant Dent Relat Res. 2018 Apr 6;20(4):531-4.
[58]. Ramesh A, Varghese S, Jayakumar ND, Malaiappan S. Comparative estimation of sulfiredoxin levels between chronic periodontitis and healthy patients - A case-control study. J Periodontol. 2018 Oct;89(10):1241-1248.Pubmed PMID: 30044495.
[59]. Ramadurai N, Gurunathan D, Samuel AV, Subramanian E, Rodrigues SJ. Effectiveness of 2% Articaine as an anesthetic agent in children: randomized controlled trial. Clin Oral Investig. 2019 Sep;23(9):3543-50.
[60]. Sridharan G, Ramani P, Patankar S, Vijayaraghavan R. Evaluation of salivary metabolomics in oral leukoplakia and oral squamous cell carcinoma. J Oral Pathol Med. 2019 Apr;48(4):299-306.
[61]. Mathew MG, Samuel SR, Soni AJ, Roopa KB. Evaluation of adhesion of Streptococcus mutans, plaque accumulation on zirconia and stainless steel crowns, and surrounding gingival inflammation in primary molars: randomized controlled trial. Clin Oral Investig. 2020 Sep;24(9):1-6.Pubmed PMID: 31955271.
[62]. Samuel SR. Can 5-year-olds sensibly self-report the impact of developmental enamel defects on their quality of life? Int J Paediatr Dent. 2021 Mar;31(2):285-286.Pubmed PMID: 32416620.
[63]. R H, Ramani P, Ramanathan A, R JM, S G, Ramasubramanian A, et al. CYP2 C9 polymorphism among patients with oral squamous cell carcinoma and its role in altering the metabolism of benzo[a]pyrene. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020 Sep;130(3):306-312.Pubmed PMID: 32773350.
[64]. Chandrasekar R, Chandrasekhar S, Sundari KKS, Ravi P. Development and validation of a formula for objective assessment of cervical vertebral bone age. Prog Orthod. 2020 Oct 12;21(1):38.Pubmed PMID: 33043408.
[65]. Vijayashree Priyadharsini J, Smiline Girija AS, Paramasivam A. In silico analysis of virulence genes in an emerging dental pathogen A. baumannii and related species. Arch Oral Biol. 2018 Oct;94:93-98.Pubmed PMID: 30015217.