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Factors Associated with *Streptococcus mutans* Pathogenicity in the Oral Cavity

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Abstract: Oral streptococci are the oral microbial flora that can cause biofilm formation. One of the most common isolated oral streptococci is *Streptococcus mutans*, which has a significant role in oral diseases, including periodontal. The most important factor of *S. mutans* pathogenesis includes biofilm formation that leads to emptying tooth enamel and caries. Various genes including atpF, gtfB, gtfC, gtfD, gtf, LuxS, comAB, comCDE, and comX regulate biofilm formation. Therefore, in this review, we aimed to investigate factors that influence *S. mutans* pathogenicity in the mouth. The main factors are related to the biofilm formation of this bacteria and metabolic products, which influence environmental changes by carbohydrate metabolism and help this pathogen to make dominant growth compared to other bacteria living in the oral cavity. Indeed, developing methods to inhibit biofilm formation and quorum sensing using antimicrobial agents with anti-biofilm and antibacterial properties should be considered based on our knowledge of the pathogenicity mechanisms of S.mutans.

Keywords: *Streptococcus mutans*; oral bacteria; biofilm; infection.

1. Introduction

Oral streptococci are components of the oral microbial flora that can cause biofilm formation [1, 2]. One of the most common isolated oral streptococci is *S. mutans*, which has an integral role in the infection of oral diseases, including periodontal [3, 4]. Biofilm-forming bacteria could cause periodontitis, an inflammatory disease resulting from infection in the gingivae, the bone around the tooth, and underlying connective tissue [5, 6]. Therefore, it is a common public health problem in children and adults [7, 8]. The causes of *S. mutans* pathogenesis include biofilm formation, changes in various proteins, synthesis of extracellular polysaccharides, and acid production, which lead to emptying tooth enamel and caries [9, 10]. So, this review will analyze factors that influence *Streptococcus mutans* pathogenicity in the mouth; therefore, we can generate useful combat with this infection. The review was conducted based on a search of scientific databases, including PubMed and Scopus, based on keywords including *S. mutans*, pathogenicity, oral, mouth, biofilm, metabolism, and infection.

2. Biofilm Formation

Biofilm is a unique microbial cell structure, enclosed by an extracellular matrix or exopolysaccharide (EPS), proteins, and nucleic acids [8, 11, 12]. The biofilm can enclose bacteria, supply food and nutrients for them, and causes resistance to antimicrobial substances, host attack, stress, and force. In addition, the biofilm can tolerate acidic environments, damaging tooth enamel and decay [12, 13]. Biofilm formation takes place in several stages: (i) production of the acquired pellicle or conditioning film on the enamel surface (ii) cell-to-cell interactions of late colonizers bacteria with each other (iii) subsequent attachment of the cell to the surface of primal colonization [14, 15]. Biofilm production begins with the interactions between the surface and planktonic bacteria in reply to suitable environmental stimuli [16-19]. In addition to responding to chemical and physical signals, various physiological functions are controlled in bacterial cells through quorum sensing [17, 20-23]. The modulation of gene expression is facilitated by the Quorum sensing signals in biofilm [24, 25].

The cariogenic functions of *S. mutans* biofilms are controlled by various genes, most of which participate in multiple basic characteristics. Avilés-Reyes *et al*. [26] have shown that *S. mutans* binds to tooth surfaces by sucrose-dependent adhesion. Within the non-attendance of sucrose, particular substrate and the adherence of surface adhesins such as SpaP are identified by the independent sucrose mechanism (Figure 1).

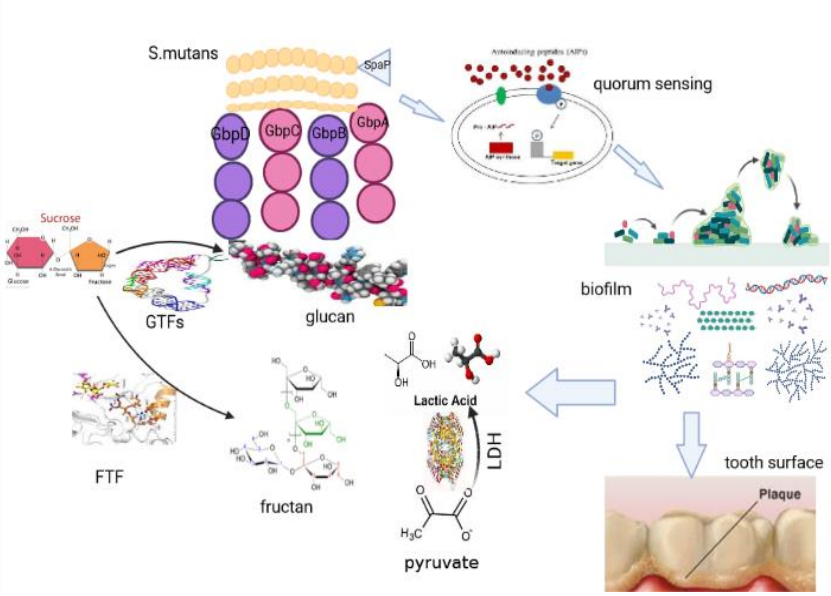

Figure 1. Biofilm formation. Adherence of surface adhesins, such as SpaP, resume biofilm formation. In another pathway, in the presence of sucrose, the glucosyltransferases (GTFs), produce water-insoluble or water-soluble glucans. Fructosyltransferase (FTF) is able to catalyze the production of fructan from sucrose. Glucan-binding proteins (GbpB) intercede bacterial interaction with extracellular glucans. Lactate dehydrogenase (LDH) catalyzes the regeneration of pyruvate to lactic acid.

In the presence of sucrose, the glucosyltransferases (GTFs), GTFB, GTFC, and GTFD produce water-soluble or water-insoluble glucans [27,28]. Fructosyltransferase (FTF) catalyzes the production of fructan from sucrose. Guan *et al*. [29] have shown that the fructan polymers are primarily used to store extracellular nutrients that may be used during times of food poverty by *S.mutans*. Glucan-binding proteins (Gbp), encoded by the *gtf* genes, could be enzymatic proteins whose glucan-binding properties help maintain it cell-associated in the lack of a cell-wall anchor [30]. The GbpB protein mediates the interaction of bacteria with extracellular

glucans. The Gbp proteins play an important role in biofilm formation and sucrose-dependent adhesion and help maintain a symbiotic and stable microbial population in the oral cavity [31].

The pyruvate production of lactic acid is catalyzed by Lactate dehydrogenase (LDH), encoded by the *ldh* gene [32]. Biofilm and acid tolerance are firstly associated with the activity of membrane-bound F-ATPase (H+ translocating ATPase), encoded by the *atpF* gene. The F-ATPase maintains cytoplasmic pH homeostasis by making the internal pH more alkaline than the ambient pH and moving proton out of cells changes [29].

3. Sucrose-Dependent Mechanism

3.1. Glucosyl transferases (Gtfs).

The most important mechanism behind dental plaque formation is glucans' production by glucosyltransferases (GTFs) [31, 33-35]. The Gtfs possess sucrose-dependent activity that causes glycosidic bond breakage and releases fructose and glucose [35]. The glucose portion is then attached to a developing polymer of glucan [36]. Glucosyltransferases (GTFs) mediate glucan synthesis from sucrose. Therefore, the glucans allow bacteria to attach to the tooth surface and each other, shaping microcolonies and enhancing biofilm formation [31, 34, 37, 38].

S. mutans synthesizes 3 types of Gtfs (GtfB, GtfC, GtfD), whose agreeable activity is regarded to be fundamental for its cellular adherence to the tooth surface [39, 40]. The GTFB, GTFC, and GTFD enzymes are encode by *gtfB*, *gtfC*, and *gtfD* genes, respectively [39, 41, 42]. The water-insoluble glucan, which is wealthy in α 1,3- glucosidic linkages, is usually synthesized by GTFB and GTFC. While the water-soluble glucans, which are rich in an α 1,6 glucosidic linkages, are synthesized by GTFD [39, 43-45]. A comparative structure presents that 75% of amino acid arrangements of the GTFB are profoundly homologous to GTFC, and 50% of the sequence of GTFD has an identity to GTFB and GTFC [40].

All Gtfs possess three particular spaces: the C-terminal glucan-binding (GB) space, the exceedingly preserved catalytic space, and the N-terminal variable junction space [35, 46]. It has appeared that GTFC plays a critical role in the generation of adhesive glucans that make a strong adherence of *S. mutans* to the surfaces [47-49]. Fujiwara *et al*. [50] demonstrated that the nucleotide deletions of the *gtfB* and *gtfC* genes reduce the biofilm formation with negligible aggregation of *S. mutans* and polysaccharides *in vitro*. Therefore, inhibition of Gtfs in solution and after adsorption to the tooth surface could be a successful method to prevent tooth decay and other biofilm-related diseases.

3.2. Glucans binding of proteins (Gbps).

Another sucrose-dependent component is Gbps, which is involved in the binding of *S.mutans* to glucans [34, 51]. *S.mutans* synthesizes at least 4 glucan-binding proteins (Gbps), including GbpA [52], GbpB [53], GbpC [54], and GbpD [55], which presumably promote the adhesion of the organisms and biofilm formation. The functions of Gbps are associated with altered biofilm production [56], cell wall solidness, peptidoglycan hydrolase action [57], dextran-dependent accumulation [54], and lipase action [55].

GbpA was firstly identified by Russell *et al*. [58]. It contains 563 amino acids and 59kD molecular weight [59]. The carboxyl-terminal of GbpA and GbpD is identical to the glucan binding domains of the GTF enzyme. In addition, GbpA require α-1,6 linkages for adhesion [31]. This protein facilitates cellular linkage to the surface and has appeared to involve in the

cariogenicity of *S. mutans* both *in vivo* and *in vitro* [60]. GbpA, GbpC, and maybe GBPs involve in the optimal aggregation and design of plaque biofilm [30]. A deformity of GbpA causes changes in biofilm architecture, including spreading of the microclone over the substratum and height reduction, as well as changes in localized PH compared to non-defective parent strain [61]. The shelter bacteria could expose to acid and make them susceptible to gene introduction because of a change in the architectures of the biofilm [59].

GbpB was the second Gbp identified by the affinity column experiments by smith *et al*. [59]. The GbpB was immunologically different in size and purification properties from other Gbps produced by *Streptococcus sobrinus* and *S. mutans* [51, 53, 62]. It has also been shown to be similar to a peptidoglycan hydrolase from group B streptococci, showing that GbpB plays a role in the production of peptidoglycan [62]. Therefore, GbpB probably is an enzyme that glucan-binding property helps maintain its cell-associated in the lack of a cell-wall anchor [30]. On the other hand, the glucan binding of GbpB may be an artifact; its primary ligand probably resides inside the cell wall [30]. Mattos-Graner *et al*. [62] demonstrated that DNA polymorphism and consequently amino acid changes were confined to the central region of the *gtfB* gene in the clinical isolates of *S.mutans*, suggesting functional conservation within the carboxyl and amino terminus of the GtfB protein.

Most of the sequence changes are identified in the central region of the *gbpB* in the restriction fragment length polymorphism (RFLP) examination of 44 amplitypes of *S. mutans*. Therefore, it indicates the maintenance of functional sequences in the C-terminal and N-terminal domains. Mattos-Graner *et al*. [62] demonstrated that *gbpB* depletion distinctly changed the early stages involved in cell division and other physiological processes of sucrose-dependent biofilm formation, which are required for the transition from planktonic growth to biofilm [4, 34].

GbpC was reported by Sato *et al*. [30]. GbpC can be a cell surface-associated protein and has been shown to develop dextrin-dependent aggregation (DDAG) *in vitro* under stressful conditions [55, 59, 62, 63]. The GbpC contains a cell-wall attachment and membrane anchor site according to cell surface expression [30, 64]. The GbpC protein (and possibly GbpB) serves as a main receptor for glucan and binds to the bacterial cell wall [65]. In addition, GbpC is similar to the antigen I/II (Ag I/II) family of proteins [66, 67]. In addition, the loss of GbpC decreases the biomass and accumulation of bacteria in the biofilm formation, which indicates GbpC is the major glucan receptor [59, 68].

GbpD was isolated and detected using a complete and detailed sequence analysis of *S. mutans* strain UA 159 [55]. GbpD has lipase action [55]. The Gbp proteins such as GbpA and GbpD possibly have evolved from Gtfs and retained the binding domain to glucan, but with a more prominent adaptation to advance higher tendencies for glucan [69]. Shah and Russell [55] demonstrated three 'alanine' repeats in the middle of the GbpD sequence, and GbpD binds to dextran with a KD of 2-3 nM. The alanine replication site is necessary for binding, confirmed by the construction of truncated GbpD derivatives [55]. GbpD contains an oxyanion hole and a GXSXG active location lipase box. In the presence of calcium, the GbpD releases free fatty acids (FFAs) from a range of triglycerides, which indicates lipase function [55]. Like GbpA, the GbpD helps the cohesiveness of adhesion and aggregates to tooth surfaces [70]. However, the loss of GbpA is comparable to a biofilm falling and spreading on the substrate, while the loss of GbpD weakens the biofilm cohesion, which leads to a decrease in height and loss of biofilm [59].

4. Sucrose-Independent Adhesion

The first step in the pathogenic process is attachment to host tissues, usually performed through proteins on the bacterial surface. The attachment is mediated by sucrose-dependent and sucrose-independent adhesion mechanisms in *S.mutans* [71]. The sucrose-independent adhesion mechanism is thought to be most significantly affected by antigen I/II (known as SpaP, Pac, P1), a 185KDa surface protein in *S.mutans* [72]. The sucrose-independent mechanism is not related to the pathogenicity of *S. mutans*. This mechanism shows an interaction between salivary agglutinin and the constituent particles of S.mutans [73-75]. Six particular locales are detected in genetic sequences encoding Ag I/II. The alanine-rich locale and proline-rich locale are the most important locales. The valine Locale is found between the A and P locale and in most of the various sequences in individual strains [76]. The proline wealthy and wealthy alanine spaces are thought to be capable of interacting with salivary components and antigen I/II [75, 77-79].

It is a domain immune antigen that is able to stimulate the antibody response and T cell proliferation [72, 80]. Salivary agglutinin, called gb340, is present in human saliva and regulates the accumulation of *S. mutans* through the P protein [73, 81]. The biofilm formation of the Ag I/II deficient mutants is reduced by 65% compared to the wild type. As well as a diminishment in its ability to advance the aggregation and attack of the dentin of the collagen-dependent [70, 82]. The Ag I/II virulence has been regarded as a hopeful target antigen for anticaries vaccines and investigated in a gnotobiotic rat model [83-86].

5. Quorum Sensing

Producing biofilm is resumed by interactions between the oral surface and planktonic bacteria in reaction to the environmental signal [17, 87-89]. *S. mutans* metabolize carbohydrates for adhesion and biofilm formation on tooth surfaces [70, 90]. Numerous factors are associated with biofilm formation, such as coaggregation adhesion and nutrient flow, which can affect gene expression and growth rate [91]. Quorum sensing is an important mechanism associated with adapting bacteria to their environment [92].

Quorum sensing interacts by producing, releasing, identifying, and responding to molecules such as partial hormones called self-inducers to coordinate their behavior in a cell density-dependent state [93]. Quorum-sensing signal molecules are little organic molecules, especially N-acyl-homoserine lactones (AHLs) in gram-negative bacteria [20, 94]. In contrast, it is oligopeptides called autoinducing peptides (AIPPs) in gram-positive bacteria. The LuxS gene is carried by *S. mutans* and other oral bacteria [95-97], which synthesizes the autoinducer-2 (AI-2) (LuxS) (autoinducer-2 system). The AI-2 is one of bacteria's foremost broadly interspecies signaling molecules [97-99]. Different virulence factors are controlled by quorum sensing in *S.mutans*, which includes a two-component signal transduction system (TCSTS).

The TCSTS consists of a membrane-bound histidine kinase (HK) sensor protein and a cognate cytoplasmic responding controller (RR) protein (Figure 2). The HK protein identifies a particular impulse and the RR protein empowers cells to respond to diverse stresses/ changes through the regulation of gene expression [100-102]. This signaling system's full function includes the *comCDE*, *comAB*, and *com X* genes [103-105]. The producing and responding to the competence-stimulating peptide (CSP) are encoded by the *comCDE* gene found in the same locus [19, 70, 106]. The *comC* encodes the precursor csp. Whereas the *comD* gene encodes HK of TCSRS and the *comE* gene encodes its cognate response controller (RR) [29, 97, 105]. The

comX gene encodes an altered sigma factor that transcribes a number of genes needed to absorb and receive foreign DNA [104]. A critical CSP concentration reacts with the HK adjacent cells and activates the *comE* through autophosphorylation.

Phosphorylated *comE,* in succession, triggers its target gene. The signaling cascade for genetic merit is probably activated by the *comCDE, comAB,* and *comX* gene. The Com system regulates the biofilm formation and biofilm architecture of the *S. mutans* [105]. The quorum sensing system acts well when cells are actively growing in biofilm, indicating that this cell-to-cell signaling system may play an important role in forming *S. mutans* biofilms [107]. Napimoga *et al*. [108] Recent studies have described the relationship between biofilm formation and the mutations at several *com* loci. They demonstrated that the inactivation of any genes encoding the components of the quorum sensing system, specific comC, produces an eccentric biofilm.

6. Acidogenicity

S. mutans is able to produce acid in the oral cavity [109]. This organism can synthesize lactate, acetate, and ethanol through the glycolytic pathway [103]. The exact distribution of fermentation products will depend on development conditions, with lactate being the major item when glucose is plenteous [110]—lactate dehydrogenase (LDH) enzyme convert propionate to lactate [110].

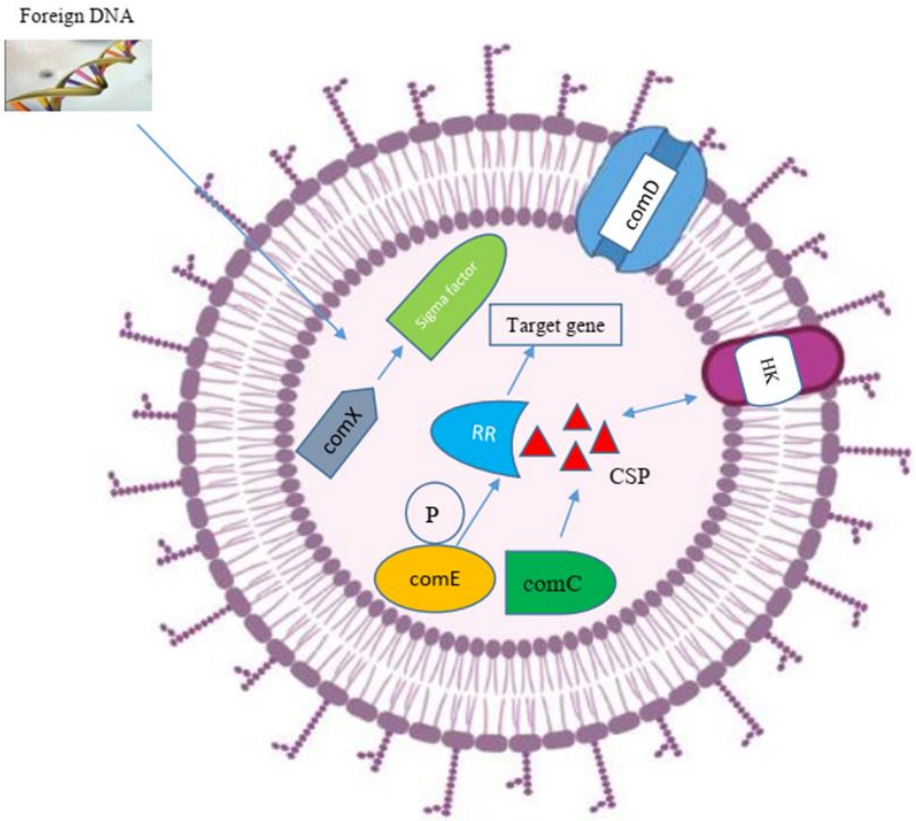

Figure 2. Quorum sensing. The HK protein identifies a particular impulse and the RR protein empowers cells to respond to diverse stresses/ changes through the regulation of gene expression. The *comC* encodes the precursor csp. Whereas the *comD* gene encodes HK and the *comE* gene encodes RR. The *comX* gene encodes an altered sigma factors that transcribes a number of genes that are needed to absorb and receive foreign DNA. A critical CSP concentration reacts with the HK adjacent cells and activates the *comE* through autophosphorylation. Phosphorylated comE, in succession, triggers its target gene. HK: histidine kinase, RR: responding controller, CSP: competence-stimulating peptide.

The strains lacking LDH display reduce caries, and the absence of LDH is lethal. However, *S. mutans* produce ethanol, acetate, and formate, when the amount of carbohydrates is limited [111-113]. Since acid is synthesized in large quantities by *S. mutans*, it seems to be an important factor in the incidence of caries [114]. In addition to sucrose, sugars in foods such as galactose and glucose can cause caries [114]. However, these sugars cause fewer caries than sucrose, regenerate to acidic metabolites, and are regenerated to extracellular polysaccharides [114]. Starches are less cariogenic than sugar because they can't easily spread into plaque. They are also less hydrolyzable [115]. In most cases, the acid production rate of S. mutans, when tested at a pH range of 5.0 to 7.0, is higher than other oral streptococci [116]. The plaque pH is decreased by consuming fermentable carbohydrates from the decaying flora compared to healthy plaque flora. Therefore, the recovery to neutral pH takes a long time. The production of dental caries and the demineralization of enamel are supported by constant plaque pH values below 5.4 [117-119].

7. Acid-tolerance

Another ability of *S. mutans* is to tolerate and survive the high amount of acid [120]. *S. mutans* retains glycolytic properties at pH levels that are development inhibitors (as low as pH 4.4) [121]. An F1F0-ATPase proton pump encoded by the *atpD* gene generally intervenes in the acid tolerance of *S. mutans* but also includes adjustment with an accompanying change in the expression of proteins and genes [97, 121, 122]. The F1F0ATPase system flushes H+ out of bacteria to maintain acid tolerance and overcome acid stress [90, 120, 123]. In addition, another function of F1F0-ATPase is ATP synthase [90]. The interior of bacteria cells keeps neutral pH, but a proton gradient is formed on the boundary of the cell membrane when the pH is more in the exterior of the cell. A motive force of the proton is caused by the proton gradient when H+ tries to enter from the cell's exterior. F1F0-ATPase uses the motive force of the proton to synthesize the ATP required for bacteria [123]. Furthermore, the agmatine deiminase system (AgDS) produces ATP, CO_2, and ammonia and is able to maintain acid tolerance and overcome acid stress.

8. Diet

Diet plays a significant part in the development of cariogenic etiopathogenesis. However, sugar consumption and decreasing sugar consumption in the diet have been focused on controlling caries [124]. The cariogenicity of meals is controlled by the content of carbohydrates as well as by the frequency with which they are consumed [125]. The main carbohydrate sources are sugars, which can combine multiple sugars in the bacterial cytoplasm. Bacteria use the sugars and serve for the production of ATP via glycolysis and synthesis of bacterial components such as nucleic acids, lipoteichoic acid, other needed polysaccharides, and peptidoglycan [126-129]. Fermentable carbohydrate is firstly sucrose, but all carbohydrates are generally assumed cariogenic [130].

Of the sugars in the diet, sucrose plays the most important role in cariogenic potential. In addition to fermentation by oral bacteria, sucrose increases the ability to colonize and grow oral bacteria such as *S. mutans*. In addition, sucrose serves as a substrate for producing EPS in dental biofilms. Sucrose is involved in mass formation, stability of the biofilm matrix, and physical integrity [131]. However, foods that involve extensive mastication, such as starchy foods and fresh fruits, cause a low cariogenic potential because of the stimulation of saliva

production [114]. The oral bacteria can decompose sugars of the food and synthesize them, glucans which have importance in interactions between cariogenic organisms and tooth enamel [31].

Various sugars could be consumed by *S. mutans*. In addition, sugars and amino sugars are used and diffused in bacterial components' glycolysis and biosynthesis pathways [132]. Disruption of this regulation causes a change in the virulence of *S. mutans*. In sugar metabolism, catabolite control protein A (CcpA) modulates the expression of numerous virulence factors *in Staphylococcus aureus and S. mutans*. Therefore, sugar metabolism is involved in bacteria's physiology and virulence [133].

Nutrition and diet play an important role in childhood decay [134]. Human milk provides nutrition and immunity in infants, and there is a dietary shift from a liquid diet and solely milk to a modified adult diet in the first few years after birth. In addition, breastfeeding and limiting night bottle feeding reduces the risk of breastfeeding caries [135]. Therefore, it is required early safety measures like properly brushing teeth, utilizing fluoride, and eating nutritional foods [127]

Cariogenic strength is increased during sleep because the acid activity derived from the metabolism of sugars is increased, and saliva excretion is decreased [136]. The noteworthy impact of fruit juice and sparkling drinks on dental caries advancement in teenagers and children has also been reported [137]. Therefore, diet drinks and energy drinks contain citric and phosphoric acids that destroy tooth enamel [138]. Tooth decay is related to the absorption of sugar in the diet [139]. Increased urbanization has caused the replacement of refined sugars with natural sugars, which has worsened the situation [139]. Many studies have shown a linear relationship between sugar intake and tooth decay in global populations [140, 141].

9. Saliva

Saliva has a significant role in oral health, Which includes regulating, maintaining, and strengthening hard and soft oral tissues [142]. The salivary glands produce saliva, including sublingual parotid, submandibular, and numerous small salivary glands [143]. Saliva secretion is a process with two stages, at the first step, the acinar cells secrete an aqueous plasma-like fluid, and in the next step, they are caused modification during transmission by the watertight ductal cell system at the next step. The autonomic nervous system regulates saliva secretion through signal transmission systems which bind receptor stimulation to ion transport mechanisms and protein secretion. The type and intensity of stimulation regulate the synthesized volume of saliva. The highest volume occurs with cholinergic stimulation. There are also several functions defined for saliva [143].

One of the important uses of saliva is to protect oral tissue from the harmful effects of microorganisms. Saliva contains a variety of proteins with antimicrobial properties. Salivary compounds, peroxidase, and lysozyme are part of the primary defense system [144]. These enzymes have bactericidal and bacteriostatic functions against different microorganisms and are present in all body secretions, such as tears and saliva [145]. The peroxidase enzyme is a glycoprotein containing porphyrin that produces the antimicrobial peroxidase system by its cofactor. Lysozyme also breaks down beta glycoside bonds in peptides and glycans, destroying the bacterial cell wall [144].

The interaction between P1-binding *S. mutans* and salivary agglutinin mediates sucrose-independent adherence and facilitates bacterial accumulation on tooth surfaces [74]. The antigen binds directly to the salivary follicle and mediates bacterial adhesion even without

sucrose. Therefore, salivary agglutinin (also known as gp340) elevates or makes bacterial clearance from the oral cavity easier, depending on its solubility or adsorption [86, 146]. The bacterium *S. mutans* uses saliva for transmission. Balakrishnan *et al*. [147] have shown a 70 percent chance of transmitting *S. mutans* from mother to infant if the level of *S. mutans* in the mother's saliva is more than 10^6/ml. In return, the chance of transmitting *S. mutans* to the infant is decreased to 20 percent if the level of *S. mutans* in the mother's saliva is less than 3×10^5/mL.

10. Sugar Metabolism

In *S. mutans*, sugars are used both extracellularly and intracellularly. Internal sugars are mostly utilized for glycolysis, the production of different components, including intercellular polysaccharides (IPS), lipoteichoic acid (LTA), and cell-walls biosynthesis. In return, external sucrose is used to produce glucans, which are extracellular polysaccharides (EPSs) [133]. Oral bacteria consume the sugars of foods and metabolize them to produce energy via fermentation and glycolysis and produce organic acids as metabolic products [148, 149].

The FTF and GTFs secreted by *S. mutans* provide attachment sites available for bacterial colonization on the tooth surfaces or bacterial binding to each other and regulate the precursor of dental caries and adherent to biofilm formation [150-152]. In addition, fucosyltransferase catalyze the synthesis of fructans and maybe energy sources [153]. Tahmourespour *et al*. [154] demonstrated that the *ftf*, gtfB, and gtfC, genes are required to bind *S. mutans* to hard surfaces through the sucrose-dependent mechanism and are potential targets for protection against tooth decay, but *gtfD* is not essential.

Fructanase (FruA) digests sucrose which is an exo-beta-D-fructosidase enzyme. The digested sucrose is used as a substrate to create fructan (β(2,1)- and β(2,6)- linked extracellular fructose polymers) and soluble (α(1,6)-linked) and insoluble (α(1,3)-linked) glucans in *S. mutans* [155]. Suzuki *et al*. [155] demonstrated that FruA has multiple effects associated with the survival functions of *S. mutans*, such as genetic transformation, bacteriocin production, and biofilm formation.

Dextran or water-soluble glucan (WSG) provides energy storage for bacteria, which has a nonlinear molecular structure and is rich in α-1,6 glucosidic linkages [156]. During glucan production, glucans undergo structural changes due to the effects of fructosyltransferases (Ftf) and GTFs, along with dextranase (Dex), a type of glucanase involved in the breakdown of WSG [157]. DexA is a WSG hydrolase, which degrades the WSG α-1,6 glycosidic bond to affect the features of dextrans and provides an energy source for bacteria. As well as it decreases the number of dextrans and has an integral effect on the production of exopolysaccharides and their chemical and physical properties [158, 159]. Its loss has also been reported with reduced virulence in some mouse models. Dextran glucosidase (DexB) cleaves the α-1,6 bond from isomalto-oligosaccharide or the nonreducing end of dextran and releases glucose [160].

The Dlt1-4 protein is responsible for the accumulation of intracellular polysaccharides as well as the storage of energy. Hence, loss of Dlt1-4 reduces pathogenicity, and its overexpression increases pathogenicity [161, 162]. The *relA* gene of *S. mutans* plays a role in regulating the phosphoenolpyruvate: carbohydrate phosphotransferase system (PTS) [163]. The enolase of *S. mutans* is a major component of the PTS that facilitates the absorption of bacterial sugar uptake [123]. Furthermore, lactic acid dehydrogenase *S. mutans* facilitates lactic acid production [149, 164].

11. Bacteriocin

Bacteriocins are antibacterial proteins synthesized by a number of bacteria to prevent or inhibit other bacteria [114]. *S. mutans* synthesizes mutacin, which is active against non-streptococcal Gram-positive bacteria and other streptococcal species [114, 165]. The mutacin production helps effectively colonize and establish *S. mutans* inside the oral cavity [166]. Rogers [166] demonstrated that 70% of *S. mutans* synthesize one or more bacteriocins.

Mutacin synthesis is controlled by two main systems: Rgg-like regulators and LytTR regulatory system [167]. The lantibiotic mutacin is controlled by mutR, a Rgg-family controller present in the gene cluster of the mutacin I, II, and III loci. They regulate the transcription of mutacin operons, but their exact role has not yet been reported. The non-lantibiotic mutacin production is regulated by the CSP- induced factors. [97, 168].

The ComCDE TCSTS play a critical role in regulating a variety of non-lantibiotic bacteriocins in *S. mutans*. Phosphorylated ComE then activates gene expression by its target bacteriocin promoters, leading to a dramatic increase in bacteriocin production [169-173]. In the lantibiotic-producing bacteria, the same lantibiotic biosynthesis operon produces bacteriocin immune proteins (Bip) to protect themselves from the harmful effects of their lantibiotics [174-176]. In general, the Bip protects the bacteria against specific classes of antimicrobial agents and often increases stress tolerance [70, 174].

12. Conclusion

In this review, we aimed to investigate factors that influence *S. mutans* pathogenicity in the mouth. The included articles' review revealed that *S. mutans* established infections and periodontitis through its virulence factors. The most important factor of S. mutans pathogenesis includes biofilm formation that leads to emptying tooth enamel and caries. The cariogenic functions of *S. mutans* biofilms are regulated by various genes. The studies showed that inhibition of some virulence factors could be a successful method of preventing tooth decay and other biofilm-related diseases. Therefore, increasing knowledge of the mechanism of pathogenicity and virulence factors is helpful for public health in prevention, diagnosis, and therapy. However, there are many issues that remain to be understood. Therefore, the pathogenesis mechanism of these factors in oral infections and periodontitis associated with *S. mutans* needs to be studied more to produce new methods for the therapies of *S. mutans* – related diseases, as well as new possible mechanisms to remove *S. mutans*.

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Conflicts of Interest

The authors declare no conflict of interest.

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