Available in PDF format.
gas is also highly produced in oral cavity and has been numerously associated with the progression of oral diseases. H$_2$S is produced both endogenously by oral cells and exog- enously through the activities of oral microbes. Understand- ing the importance of this gas in the progression of oral diseases is of greater importance due to its activities in cell regulation. Therefore, in this review article, we will discuss the molecular mechanisms associated with the production and utilization of H$_2$S and correlate the dysregulation of this gaseous neuromodulator with oral diseases.

2. **H$_2$S Production in Oral Cavity**

2.1. *Endogenous H$_2$S Production in Oral Cavity*. The endog- enous production of H$_2$S is principally catalyzed by three enzymes, namely, cystathionine gamma-lyase (CSE), cystathionine beta-synthase (CBS), and 3-mercaptopyruvate sul- fur transferase (3-MST). The former two are members of the pyridoxal 5’-phosphate (PLP-) dependent enzymes and are known to be involved in the metabolism of amino acids. CSE and CBS have been reported to be significantly expressed in gingival tissues at both gene and protein levels [7]. At cellular level, the two enzymes have also been identified to be the main producers of H$_2$S in human periodontal ligament [8]. 3-MST is also strongly expressed in oral tissues. In oral cavity, H$_2$S participates in the regulation of cel- lular homeostasis. For instance, gingival crevicular fluid (GCF) volume which is an important parameter of oral health has been positively correlated with clinical features such as inflammation [9]. Simultaneously, the GCF volume significantly correlates with both the production of H$_2$S by the cervical fluid and the rate of inflammation [10]. The above data confirms the production of H$_2$S in oral cavity by different sites and its involvement in oral health.

2.2. *H$_2$S Production by Oral Bacteria*. Apart from endoge- nous production, bacteria present in the oral cavity synthe- size H$_2$S through several enzymatic reactions. Some of these enzymes include CSE, CBS, and 3-MST [11–13], cyste- ine desulfurase (CD) [14–18], lanthionine synthase (LS) [19–23], aspartate aminotransferase [21, 24], l-methionine gamma-lyase (MGL) [21, 25–28], and cysteine hydroxyyl lyase (CHL) [21, 29]. Through different mechanisms, these bacteria-contained enzymes catalyze the production of H$_2$S from multiple substrates (Figure 1).

3. **H$_2$S-Regulated Cellular Mechanisms in Oral Cavity**

3.1. *Oxidative Stress*. Oxidative stress is one of the com- monly dysregulated entities and a potential therapeutic tar- get in chronic oral diseases [30, 31]. Oxidative stress is caused by an imbalance between oxidants and antioxidant levels which result into protein, lipids, DNA, and RNA oxida- tion and damage. In oral cavity, oxidative stress can be induced by many factors including cigarette smoking [32], metabolic diseases [33], hydrogen peroxide- (H$_2$O$_2$-) based tooth whitening products [34], food [35], and most impor- tantly from oral bacteria [36–38]. High oxidative stress leads to the promotion of senescence-like features [39] and progres- sion of oral diseases [40, 41]. In human cellular models, the bacterial-produced H$_2$O$_2$ have been demonstrated to be lethal to both epithelial and macrophage cells [42, 43]. With regard to H$_2$S, previous studies indicate that exogenous H$_2$S can promote reactive oxygen species (ROS) generation and subsequently DNA damage in both human gingival epithel- ial cells and keratinocyte stem cells [44, 45]. Meanwhile, in oral bacteria, both pro- and antioxidative properties have been reported in bacteria following H$_2$S treatment which suggests that its subsequent effect varies in different conditions. For example, in bacteria *S. aureus*, the inhibition of H$_2$S-synthesizing enzymes can potentially increase their vul- nerability to immune defense and antibiotics [46, 47], indic- ating the protective role of the compound, whereas in a non-H$_2$S-synthesizing bacteria *A. baumannii*, exogenous H$_2$S improves the sensitivity of the bacteria to numerous antibiotics by targeting redox status and energy metabolism [48]. Regardless, these data imply that H$_2$S plays a crucial role in bacteria survival, and exogenous H$_2$S might promote the oxidative stress features in the host cell meanwhile inducing a similar or a protective effect in bacteria depend- ing on the redox status (Figure 2).

3.2. *Apoptosis*. Apoptosis is a programmed mechanism involved in the regulation of body homeostasis by system- atically killing cells that are no longer needed. The dys- regulation of this process can lead to excessive cell death (e.g., in tissue fibrosis) or the vice versa (e.g., in cancer). Apoptosis is triggered through the activation of a group of protein known as caspases (Casp) in intrinsic- or extrinsic-dependent signaling pathways. Previous studies show that the treatment of H$_2$S derived from either exog- enous sources or a pathogenic oral bacteria *T. denticola* can significantly induce apoptosis in oral cells including the human periodontal ligament cells (PDLCs) and human gingival fibroblasts (HGFs) [49, 50]. The induction of apo- ptosis by oral H$_2$S is mediated via mitochondria dependent pathway as evidenced by the promotion of Casp-3, Casp-8, Casp-9, cytochrome c, mitochondria depolarization, and the subsequent activation of p53 signaling cascade [51–55]. Moreover, the event is associated with the elevation of proapoptotic genes such as B cell lymphoma 2 (Bcl-2), phosphatase and tensin homolog, sirtuin, histone deacetyl- ase, growth arrest, and DNA damage-inducible gamma, together with the ROS levels and DNA damage [56, 57]. However, the expression of the key component of death receptor apoptotic pathway, Casp-8, could not be affected by the increase, which suggests that the pathway is not necessarily targeted. In a recent study, the gingiva-derived mesenchymal stem cells (GMSCs) known to participate in immunomodulation and tissue regeneration have been shown to utilize CBS/CSE/H$_2$S axis in mediating the apopto- sis of regulatory T cell via the Fas/FasL signaling pathway [58]. With this crucial finding, it is essential to analyze the role of bacteria-derived H$_2$S in the function of GMSCs both in health and disease states. Moreover, the abundance of sev- eral key H$_2$S-producing bacteria in oral cavity noticeably relates with the apoptotic activities in the surrounding cells.
A recent study analyzing the role of oral microbes in oral epithelial cells death found a positive correlation between the abundance of *S. gordonii*, *S. sanguinis*, and *P. gingivalis* with elevation of apoptosis and pyroptotic activities in a mechanism involving the elevation of Casp, TNF receptor p55, apoptosis-inducing factor (AIF), proteolytic activities of gingipain enzyme, cleaved poly (ADP-ribose) polymerase (PARP), and topoisomerase 1, heat-labile protein-induced...
activation of interleukin-1β- (IL-1β-) converting enzyme and nuclear factor-kappa B (NF-κB), and partial activation of protein kinase B (AKT)/mitogen-activated protein kinase (MAPK) cascades [59–64].

3.3. Inflammation. Inflammation is a response mechanism to tissue/cell damage and infection. In dental pulp mesenchymal stem cells and GMSCs, inflammation is associated with higher proliferation rate [65]. Besides, human gingival tissues from periodontal patients show improved expressions of inflammatory markers such as tumor necrosis factor-α (TNF-α), interferon gamma (IFN-γ), and interleukins (ILs) [66]. Inflammation strongly correlates with the decline in vitamin D; hence, an increase in vitamin D can suppress both pathogenic invasions and inflammatory responses in human gingival epithelial cells [67]. LPS from bacteria also induces the release of proinflammatory IL-6 and IL-8 in HGFs which maintain the release upon further treatment with LPS indicating lack of tolerance [68]. Mechanistically, it is suggested that P. gingivalis LPS binds to the Toll-like receptor 4 (TLR4) to mediate the downstream regulation of inflammatory activities [69]. In mouse abscess model, H₂S from P. gingivalis has been reported to only enhance the inflammatory effect induced by CH₃SH [70]. With respect to lifestyle, electronic cigarettes with flavorings are associated with high proinflammatory activities and oxidative/carbonyl stress in oral cells [71] and the use of fixed orthodontic devices with poor oral hygiene, high levels of H₂S, and proinflammatory activities in children [72]. A previous study suggests that treatment with NaHS aggravates the proinflammatory activities of P. gingivalis in HGFs and PDLCs by activating the NF-κB pathway [73]. Meanwhile, the treatment with GYY4137 in oral mucosa wound reduces the induced macrophage activation and restores the diminished H₂S levels and prevents the polarization of macrophage 1, suggesting a potential anti-inflammatory influence of the slow-releasing donor [74]. Similarly, in HGFs, the treatment with diallyl sulfide significantly reduces the LPS-induced elevation of TNF-α, IL-1β, IL-6, and NF-κB levels [75]. Overall, these data suggest that H₂S may have pro or anti-inflammatory responses in oral cells. Although, the leading factors need to be further determined.

4. H₂S and Oral Diseases

4.1. Oral Malodour (Halitosis). Halitosis is a common medical condition of the oral cavity associated with the psychological and physical discomfort as a result of an offensive bad breath. H₂S, (CH₃)₂S, and CH₃SH are the main compounds causing the condition. Halitosis can be classified as intraoral or extraoral depending on the origin of the compounds. H₂S and CH₃SH are the common components of the former type, whereas (CH₃)₂S features the latter [76]. Extraoral halitosis can be further subdivided into bloodborne or nonblood borne originating from the respiratory tracts or blood, respectively. Intraoral halitosis is caused by several factors including oral bacteria and diseases [77]. Mimicking intraoral halitosis by treating rat epithelial cells with low concentrations of H₂S gas for 50 days results in significant changes in cellular structure, vacuolization, and loss of intercellular matrix resembling halitosis in human [78]. An increase in the abundance of H₂S-producing oral bacteria in oral biofilm has been associated with the disease [79]. In a recent study, both oral malodorous compounds (H₂S, CH₃SH, and (CH₃)₂S) and bacteria diversity have been reported to be higher in halitosis patients compared to normal individuals [80, 81]. Among others, the genera Peptostreptococcus and Alloprevotella together with the specie Eubacterium nodatum are highly abundant in halitosis patients and positively correlate with H₂S and CH₃SH concentrations in adults [82]. Similarly, in children with halitosis, evidences indicate that the rate of production/consumption of H₂S is high as compared to healthy subjects [83]. However, the use of mouth-rinsing products could effectively reduce H₂S levels in halitosis patients [84] (Figure 3). Together, these data show that oral bacteria are associated with halitosis through their involvement in the production of H₂S. Also, H₂S contributes immensely to the bad smell in halitosis and targeting this compound directly or indirectly might improve oral health and reduce the destruction of the oral tissues.

4.2. Periodontitis. Periodontitis is the common oral disease characterized by the chronic inflammation of the periodontal ligaments leading to the loss of connective tissue, alveolar bone resorption, and development of periodontal pockets. Oral bacteria play a major role in the development of this disease [85]. A qPCR analysis shows high abundance of P. gingivalis, T. denticola, and T. socranskii in plaque samples from aggressive (84, 74, and 71%) and chronic periodontitis patients (95, 94, and 89%) [86]. Antibacterial treatments inhibiting the growth of P. gingivalis have been shown to be effective in combating the disease in clinical trials [87, 88]. Similarly, periodontitis is also correlated with oral malodour in patients’ model [89]. In periodontitis patients, H₂S levels show positive association with the abundance of P. gingivalis in tongue coatings [90], and the bacteria growth together with volatile smell in the oral cavity can be suppressed with methionine gamma-lyase deaminase/CSE inhibitor PAG [91]. CBS deficiency specifically causes a condition known as homocystinuria, which is characterized by elevated of proinflammatory factors such as IL-1β, IL-6, and TNF-α. A recent study aiming to compare the periodontium of the CBS⁺⁺ mouse model to the wild type suggests a significant correlation between periodontal diseases and CBS deficiency [92]. Moreover, another study reports that supplementation of H₂S using GYY4137 promotes inflammatory and autophagic responses in LPS-treated HPDLCs and ligation-induced rats [93]. Here, GYY4137 treatment could markedly elevate the expressions of Bcl-1 and LC-3 and decrease that of p62, whereas the inhibition of the autophagy with 3-methyladenine further aggravates inflammatory activities, implying that the treatment triggers a protective autophagy in order to avert the enhanced inflammation. However, another study suggests that a H₂S-releasing ketoprofen drug, ATB-352, can prevent the LPS-induced periodontitis and associated bone resorption in rats by reducing inflammation, apoptosis, and ROS through...
attenuating the IL-1β, TNF-α, NF-κB, Bax, cyclooxygenase-2 (COX-2), and iNOS expressions, myeloperoxidase activities, and tartrate-resistant acid phosphatase positive cells as well as upregulating Bcl-2 [94]. This is consistent with the previous studies conducted using H2S donors, ATB-346, and Na2S in periodontic rat model which demonstrates the reduction of proinflammatory activities, ROS, and bone loss [95]. Meanwhile, NaHS treatment could not show any reduction or promotion of bone loss in ligature-induced rats [96, 97], although the presence of both nitric oxide (NO) and H2S moiety in ketoprofen derivatives might be the reason for the observed anti-inflammatory property. The available information suggests that the nature of the donor influences its effects, and leaves the question of the role of H2S on periodontitis unanswered. But it is possible that H2S produced by bacteria can facilitate periodontitis; however, more studies are needed to examine the mechanisms involved (Figure 4).

4.3. Dental Root Resorption (DRR). DRR is the medical condition featured by the mechanical- or chemical-induced loss of the protective tissues of the root apex structure of the tooth which exposes the tissues to bacterial infections [98, 99]. One of the common causes of DRR is orthodontic treatments, although in most cases, the condition is classified as minor or moderate. Without further stimulation or persistent inflammation, the RR can be routinely repaired [100]. Oral bacteria and their byproducts such as H2S promote inflammation and in that sense enhance the progression of DRR. To examine the influence of H2S in DRR, Lu et al. used a CSE-knockout mouse model and compared them with the wild type. The results indicate that the downregulation of CSE, which is the main H2S-producing enzyme in osteoclast, attenuates the progression of orthodontic RR [101]. Simultaneously, the reduction in mRNA levels of the RANKL and osteoprotegerin which have previously been associated with proinflammatory responses in orthodontic RR could be observed in CSE knockout mice [101, 102]. This confirms that the increase in H2S may promote the progression of the condition. However, further studies are needed to examine the influence of exogenously produced H2S in the disease.

4.4. Gingivitis. Gingivitis is an inflammatory disease primarily caused by the deposition of microbial plaque near the gingival sulcus [103]. The disease is associated with the abundance of Streptococcus, Fusobacterium, Actinomyces, Treponema, Capnocytophaga, and Bacteroides. On the other hand, the healthy gingival is characterized by species such as Streptococcus sanguis and Fusobacterium naviforme. Gingivitis occurs in two forms: acute necrotizing ulcerative and chronic gingivitis; however, chronic form is the most common one. In an earlier study, the accumulation of dental
plaque has been determined to be much greater in older individuals than younger ones possibly due to poor oral hygiene [104]. It has been reported that oral VSCs in dogs with gingivitis have a significant relationship with the amount of plaque and the severity of the disease [105]. In addition, gingival inflammation and bleeding on probing also correlate with sulfide levels in human gingival mucosae [106, 107]. Therefore, the elevation of sulfide levels as a result of the accumulation of pathogenic bacteria in gingivitis can positively influence the disease progression by promoting gingival inflammation.

4.5. Oral Cancer

4.5.1. Oral Squamous Cell Carcinoma (OSCC). OSCC is most frequently diagnosed type of head and neck carcinoma with recent global estimation of 377,713 new cases and 177,757 deaths in 2020 [108]. Despite a recent increase in incidence rate [109], the disease has a relatively stable survival rate which increased for about 8.4% from 1980s to 2010s [110]. Some of the common risk factors for the disease include excessive smoking, alcohol abuse, and oral diseases. Otherwise, oral bacteria have also been identified to be an independent risk factor for the disease in nonsmokers and oral human papillomavirus- (HPV-) negative patients [111]. Generally, in OSCC patients, key bacteria including Prevotella, Fusobacteria, Pseudomonas aeruginosa, Haemophilus influenzae, Campylobacter, Parvimonas micra, and Filifactor alocis are distinctly elevated, correlate with the stages of OSCC progression, and act on vital signaling cascades [112–116].

The analysis of punch biopsies and benign mucosae reveals that H2S is significantly upregulated in OSCC patients as compared to the control group as evinced by the increase of CSE, CBS, and 3-MST levels [117]. In addition, OSCC also contains higher levels of procarcinogenic markers such as phosphorylated signal transducer and activator of transcription-3 (p-STAT3), mitoNEET, telomerase reverse transcriptase, and MAPK. Besides, the extreme volatile malodor has also been reported in head and neck carcinoma patients and suggested to be a potential diagnostic target for the diseases, which further confirm a decisive relationship between these volatile compounds and the disease [118, 119]. It has been shown that surgical treatment of OSCC can effectively reduce the volatile malodor including
those of sulfide containing compounds commonly generated by oral bacteria [120, 121]. Using a donor NaHS, previous studies suggest that the exogenous H2S promotes the proliferation and cell cycle progression in OSCC cell lines Cal27, GNM, and WSU-HN6 through elevating the expressions of proliferating cell nuclear antigen and cyclin-dependent kinase 4 and reducing those of replication protein A 70 and retinoblastoma protein 1 via the AKT/extracellular signal-regulated kinase 1/2 (ERK1/2) pathways [121, 122]. Together, these data confirm the involvement of oral bacteria and their products including H2S in the progression of OSCC and illuminate the potential of inhibiting the production of H2S in combating this disease.

4.5.2. Oral Adenoid Cystic Carcinoma (OACC). OACC is the rare form of head and neck carcinoma of unknown etiology. The statistics show a decline in the prevalence of the disease from 1970s to 2000s [123]. Despite having a relatively high short-term overall survival which ranges from 90% in 5 years to 69% in 15 years, the disease has high recurrence rate [124, 125]. Although not 100% effective, both surgery and radiotherapy can significantly impede the progression of the disease [126]. The analysis of oral bacteria composition between OACC patients and healthy individuals indicates a considerable difference in genera Streptococci, Neisseria, and Porphyromonas [127]. In a case study of a single, 54-year-old female OACC patient, the protein expressions of the three H2S-synthesizing enzymes as well as those mitoNEET and nicotinamide phosphoribosyl transferase have been reported to be upregulated in OACC tissues as opposed to adjacent benign oral mucosa; however, the decrease in the production of H2S for over 30% could also be observed in the OACC samples, indicating that the H2S is overutilized in the disease model and might be involved in the progression of the disease [128]. So far, little is known on the role of oral bacteria and oral malodour in the development of OACC. Even though the available information suggests the involvement of H2S in the progression of the disease, the influence of exogenous H2S demands further exploration.

4.5.3. Oral Cavity Mucoepidermoid Carcinoma (MEC). MEC is one of the least-researched cancers but a highly prevalent salivary gland malignancy. The disease has relatively favourable prognosis; however, advanced age, advanced stage, and high-grade tumors negatively impact the survival rate [129, 130]. Surgery is the common treatment option for the disease. In a single-case study involving a 55-year-old woman, the expressions of CSE, CBS, and 3-MST have been reported to be elevated in MEC tissues; meanwhile, the levels of free H2S, acid labile, and bound sulfane sulfur remain the same between MEC and neighboring benign oral mucosae [130]. In addition, the study reported the elevation of key markers such as phospho-ser727-STAT-3 and Nampt that are known to promote cancer growth and metastasis as well as interact with H2S-synthesizing enzymes [131, 132]. Furthermore, the antiapoptotic and antiangiogenic protein mitoNEET has also reported to be upregulated in the metastatic tissue as compared to benign [133]. Collectively, this information indicates that H2S is highly produced and utilized in MEC and plays a crucial part in the progression of the disease. However, limited information is available on the matter, and more studies are needed to deepen the exploration.

4.6. Endodontic Treatment Failures. Endodontic treatment incorporates surgical and nonsurgical treatment options for root canal [134, 135]. The therapy involves the treatment of the infection, removal of the invading microorganisms, and perfect sealing of the canal. Despite the success of the method used, in significant cases, the treatments have been reported to fail. Some of the factors causing the failure of the therapy as identified in patients from Japan include perforation, root fracture, open apices, periodontic diseases, fenestrations, and accessory canal [136]. Apart from these factors, another key causative of endodontic failures is bacterial infection [137]. A substantial difference has been reported in patients with failed treatment as opposed to the untreated ones, with the former featured by the dominance of Enterococcus faecalis [138]. Also, bacteria such as P. gingivalis and F. nucleatum have been reported to participate in the treatment failure. With respect to H2S, previous studies indicate that VSCs specifically H2S and CH3SH can trigger proinflammatory responses in endodontic treatment failures by increasing the levels of IFN-γ and IL-10 in patients [139, 140]. This suggests that H2S produced by oral bacteria can potentially increase inflammation which in turn hinders the treatment efficacy.
5. Conclusion

H₂S is among the VSCs released by the oral microbes and strongly produced by oral cells. The upregulation of H₂S production as a result of endogenous/cellular mechanisms or exogenous/bacteria activities has significant impact in oral health. This is due to the role of H₂S in regulating cellular activities such as oxidative stress, apoptosis, cell differentiation, and inflammation. In most oral diseases, H₂S is a prerequisite for further progression and severe conditions. Besides, the reducing power of H₂S helps to suppress the effects of drugs that work primarily through promotion of oxidative stress; this is a crucial mechanism observed in antibiotic resistance by the oral bacteria. In recent years, the role of H₂S has been well documented in various diseases including cancer, heart diseases, respiratory diseases, and metabolic diseases [141–144]. Despite high production of this gas by pathogenic oral bacteria, yet few information is available concerning the matter. In chronic oral diseases such as cancers, high production and high utilization of H₂S have been reported to the extent that cancer tissues and surrounding tissues have no significant difference in H₂S levels despite high levels of the synthetase enzymes observed in cancer tissues. Also, few clinical trials are available on the subject and none of them specifically targeted H₂S alone which stresses the need for further studies to be conducted (Table 1). Therefore, it is important to examine the role of H₂S in oral diseases in order to establish literature foundation for the possibility of using this gasotransmitter as diagnostic tool or therapeutic target.

Additionally, treatment of oral diseases with H₂S donors has also been shown to have conflicting outcomes; this effect is possibly in relation to the nature of the donor used and their mechanism of actions. With regard to this, it is crucial to determine the impact of downregulation of H₂S levels in these disease models and check the possibility of combining H₂S inhibitors and other treatment options for oral diseases in order to improve the sensitivity of the therapies. One of the challenges facing the inhibition of H₂S in oral diseases especially the H₂S produced by oral bacteria is the complexity of their mechanisms. Different bacteria can produce the gas through different enzymes which affects the specificity of the available inhibitors. With further research, many challenges facing this venture will be solved. Hence, it is indispensable to examine the mechanism used by H₂S to induce its effect in oral diseases, cellular activities targeted, and outcome. Otherwise, the future advance in this field will help to clarify and improve the current knowledge available concerning H₂S and oral diseases.

Abbreviations

VSCs: Volatile sulfur compounds
LPS: Lipopolysaccharides
H₂S: Hydrogen sulfide
CSE: Cystathionine gamma-lyase
CBS: Cystathionine beta-synthase
3-MST: 3-Mercaptopropionate sulfur transferase
PLP: Pyridoxal 5’-phosphate
GCF: Gingival crevicular fluid

CH₃SH: Methyl mercaptan
(CH₃)₂S: Dimethyl sulfide
L-Cys: L-Cysteine
L-Hcy: L-Homocysteine
Cd: Cysteine desulfurase
OASS-A/-B: O-Acetylsulfine sulphydrylase-A/-B
CBL: Cystathionine beta-lyase
LS: Lanthionine synthase
MGL: L-Methionine gamma-lyase
DNA: Deoxyribose nucleic acid
H₂O₂: Hydrogen peroxide
ROS: Reactive oxygen species
GSH: Glutathione
NaHS: Sodium hydrosulfide
Casp: Caspase
PDLCs: Periodontal ligament cells
HGFs: Human gingival fibroblasts
Bcl-2: B cell lymphoma 2
GMSCs: Gingiva-derived mesenchymal stem cells
LC-3: Microtubule-associated protein 1A/1B-light chain-3
AIF: Apoptosis-inducing factor
PARP: Poly (ADP-ribose) polymerase
TNF: Tumor necrosis factor
TLR4: Toll-like receptor 4
NF-κB: Nuclear factor-kappa B
ILs: Interleukins
AKT: Protein kinase B
MAPK: Mitogen-activated protein kinase
NO: Nitric oxide
DRR: Dental root resorption
OSCC: Oral squamous cell carcinoma
HPV: Human papillomavirus
STAT3: Signal transducer and activator of transcription-3
IFN-γ: Interferon gamma
COX-2: Cyclooxygenase-2
OACC: Oral adenoid cystic carcinoma
ERK1/2: Extracellular signal-regulated kinase 1/2
MEC: Mucoepidermoid carcinoma

Conflicts of Interest

The authors declare that they have no competing interests.

Authors’ Contributions

Dong-Dong Wu and Ebenezeri Erasto Ngowi contributed equally to this work.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (Nos. 81802718 and 81670088), the Foundation of Science & Technology Department of Henan Province, China (Nos. 202102310480 and 192102310151), and the Training Program for Young Backbone Teachers of Institutions of Higher Learning in Henan Province, China (No. 2020GGJ5038).
References

[1] C. Scully, “Halitosis,” *BMJ Clinical Evidence*, vol. 2014, p. 1305, 2014.

[2] T. Wong and D. Wiesenfeld, “Oral cancer,” *Australian Dental Journal*, vol. 63, pp. S91–S99, 2018.

[3] M. K. Shirazi, A. Azarnezhad, M. F. Abazari et al., “The role of nitric oxide signaling in renoprotective effects of hydrogen sulfide against chronic kidney disease in rats: involvement of oxidative stress, autophagy and apoptosis,” *Journal of Cellular Physiology*, vol. 234, no. 7, pp. 11411–11423, 2019.

[4] J. Li, X. Teng, S. Jin et al., “Hydrogen sulfide improves endothelial dysfunction by inhibiting the vicious cycle of NLRP3 inflammasome and oxidative stress in spontaneously hypertensive rats,” *Journal of Hypertension*, vol. 37, no. 8, pp. 1633–1643, 2019.

[5] S. Kar, H. R. Shahshahan, B. T. Hackfort et al., “Exercise training promotes cardiac hydrogen sulfide biosynthesis and mitigates pyroptosis to prevent high-fat diet-induced diabetic cardiomyopathy,” *Antioxidants*, vol. 8, no. 12, p. 638, 2019.

[6] C. Szabo, C. Coletta, C. Chao et al., “Tumor-derived hydrogen sulfide, produced by cystathionine-β-synthase, stimulates bioenergetics, cell proliferation, and angiogenesis in colon cancer,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 110, no. 30, pp. 12474–12479, 2013.

[7] J. Chun-Mei, C. Wu, M. Guo-Liang, G. Yue, C. Ning, and Y. Ji, “Production of endogenous hydrogen sulfide in human gingival tissue,” *Archives of Oral Biology*, vol. 74, pp. 108–113, 2017.

[8] S. D. Cen, W. B. Yu, M. M. Ren et al., “Endogenous hydrogen sulfide is involved in osteogenic differentiation in human periodontal ligament cells,” *Archives of Oral Biology*, vol. 68, pp. 1–8, 2016.

[9] Y. B. Zhao, H. X. Meng, and Z. B. Chen, “The clinical observations and the measurement of gingival crevicular fluid volume during the experimental gingivitis,” *Zhonghua Kou qiang yi xue za zhi = Zhonghua Kouqiang yixue zazhi = Chinese Journal of Stomatology*, vol. 10, no. 1, p. 14886, 2020.

[10] S. D. Cen, W. B. Yu, M. M. Ren et al., “Endogenous hydrogen sulfide is involved in osteogenic differentiation in human periodontal ligament cells,” *Archives of Oral Biology*, vol. 68, pp. 1–8, 2016.

[11] Y. Matoba, T. Yoshida, H. Izuha-Kihara, M. Noda, and M. Sugiyama, “Crystallographic and mutational analyses of cystathionine β-synthase in the H2S-synthetic gene cluster inLactobacillus plantarum,” *Protein Science: a Publication of the Protein Society*, vol. 26, no. 4, pp. 763–783, 2017.

[12] Y. Matoba, M. Noda, T. Yoshida et al., “Catalytic specificity of the _Lactobacillus plantarum_ cystathionine γ-lyase presumed by the crystallographic analysis,” *Scientific Reports*, vol. 10, no. 1, p. 14886, 2020.

[13] A. Spallarossa, A. Carpen, F. Forlani, S. Pagani, M. Bolognesi, and D. Bordo, “Ssea, a 3-mercaptoerypyurate sulfurtransferase fromEscherichia coli: crystallization and preliminary crystallographic data,” *Acta Crystallographica. Section D, Biological Crystallography*, vol. 59, no. 1, pp. 168–170, 2003.

[14] L. Chu, J. L. Ebersole, G. P. Kurzban, and S. C. Holt, “Cystathionin, a 46-kilodalton cysteine desulphydrase from Treponema denticola, with hemolytic and hemoxidative activities,” *Infection and Immunity*, vol. 65, no. 8, pp. 3231–3238, 1997.

[15] G. P. Kurzban, L. Chu, J. L. Ebersole, and S. C. Holt, “Sulfhemoglobin formation in human erythrocytes by cystalin, an L-cysteine desulphydrase from Treponema denticola,” *Oral Microbiology and Immunology*, vol. 14, no. 3, pp. 153–164, 1999.

[16] L. Chu, Z. Dong, X. Xu, D. L. Cochran, and J. L. Ebersole, “Role of glutathione metabolism of Treponema denticola in bacterial growth and virulence expression,” *Infection and Immunity*, vol. 70, no. 3, pp. 1113–1120, 2002.

[17] R. Claesson, M. B. Edlund, S. Persson, and J. Carlsson, “Production of volatile sulfur compounds by various Fusobacterium species,” *Oral Microbiology and Immunology*, vol. 5, no. 3, pp. 137–142, 1990.

[18] H. Fukamachi, Y. Nakano, M. Yoshimura, and T. Koga, “Cloning and characterization of the L-cysteine desulphydrase gene of Fusobacterium nucleatum,” *FEMS Microbiology Letters*, vol. 215, no. 1, pp. 75–80, 2002.

[19] Y. Kezuka, N. Abe, Y. Yoshida, and T. Nonaka, “Purification, crystallization and preliminary X-ray analysis of two hydrogen sulfide-producing enzymes from Fusobacterium nucleatum,” *Acta Crystallographica. Section F, Structural Biology and Crystallography Communications*, vol. 68, no. 12, pp. 1507–1510, 2012.

[20] V. Kapral, I. Anderson, N. Ivanova et al., “Genome sequence and analysis of the oral bacterium Fusobacterium nucleatum strain ATCC 25586,” *Journal of bacteriology*, vol. 184, no. 7, pp. 2005–2018, 2002.

[21] K. Suwabe, Y. Yoshida, K. Nagano, and F. Yoshimura, “Identification of an L-methionine γ-lyase involved in the production of hydrogen sulfide from L-cysteine in Fusobacterium nucleatum subsp. nucleatum ATCC 25586,” *Microbiology*, vol. 157, no. 10, pp. 2992–3000, 2011.

[22] R. G. Mothersole and K. R. Wolthers, “Structural and kinetic insight into the biosynthesis of H2S and L-Lanthionine from L-Methionine by a Pyridoxal-Phosphate-Dependent enzyme fromFusobacterium nucleatum,” *Biochemistry*, vol. 58, no. 34, pp. 3592–3603, 2019.

[23] R. G. Mothersole, C. R. Billett, G. Saini, M. K. Mothersole, A. L. Darbyshire, and K. R. Wolthers, “S224 presents a catalytic trade-off in PLP-Dependent-Lanthionine synthase fromFusobacterium nucleatum,” *Biochemistry*, vol. 59, no. 44, pp. 4250–4261, 2020.

[24] Y. Yoshida, S. Ito, M. Kamo et al., “Production of hydrogen sulfide by two enzymes associated with biosynthesis of homocysteine and lanthionine in Fusobacterium nucleatum subsp. nucleatum ATCC 25586,” *Microbiology*, vol. 156, no. 7, pp. 2260–2269, 2010.

[25] M. Yoshimura, Y. Nakano, H. Fukamachi, and T. Koga, “3-Chloro-DL-alanine resistance by L-methionine-alpha-deaminase of an L-methionine-alpha-deaminase from Treponema denticola,” *FEBS Letters*, vol. 523, no. 1-3, pp. 119–122, 2002.

[26] Y. Nakano, M. Yoshimura, and T. Koga, “Methlyl mercaptan production by periodontal bacteria,” *International Dental Journal*, vol. 52, no. 5, pp. 217–220, 2002.

[27] M. Yoshimura, Y. Nakano, Y. Yamashita, T. Oho, T. Saito, and T. Koga, “Formation of methyl mercaptan from L-methionine by Porphyromonas gingivalis,” *Infection and Immunity*, vol. 68, no. 12, pp. 6912–6916, 2000.

[28] Y. Yoshida, K. Suwabe, K. Nagano, Y. Kezuka, H. Kato, and F. Yoshimura, “Identification and enzymic analysis of a novel protein associated with production of hydrogen sulfide and L-serine from L-cysteine in Fusobacterium nucleatum subsp.
nucleatum ATCC 25586,” Microbiology, vol. 157, pp. 2164–2171, 1999.

[29] Y. Kezuka, T. Ishida, Y. Yoshida, and T. Nonaka, “Structural insights into the catalytic mechanism of cysteine (hydroxyl) lyase from the hydrogen sulﬁde-producing oral pathogen, Fusobacterium nucleatum,” The Biochemical Journal, vol. 475, no. 4, pp. 733–748, 2018.

[30] D. A. Cherian, T. Peter, A. Narayanan, S. S. Madhavan, S. Ahammada, and G. P. Vynat, “Malondialdehyde as a marker of oxidative stress in periodontitis patients,” Journal of Pharmacy & Biomedical Sciences, vol. 11, Suppl 2, pp. S297–S300, 2019.

[31] S. S. Beevi, A. M. Rasheed, and A. Geetha, “Evaluation of oxidative stress and nitric oxide levels in patients with oral cavity cancer,” Japanese Journal of Clinical Oncology, vol. 34, no. 7, pp. 379–385, 2004.

[32] A. Z. Reznick, I. Klein, J. P. Eisierich, C. E. Cross, and R. M. Nagler, “Inhibition of oral peroxidase activity by cigarette smoke: in vivo and in vitro studies,” Free Radical Biology & Medicine, vol. 34, no. 3, pp. 377–384, 2003.

[33] A. Vicente, L. A. Bravo-González, J. A. Navarro, A. J. Buenf, and F. Camacho-Alonso, “Effects of diabetes on oxidative stress, periodontal ligament ﬁber orientation, and matrix metalloproteinase 8 and 9 expressions during orthodontic tooth movement,” Clinical Oral Investigations, vol. 25, no. 3, pp. 1383–1394, 2021.

[34] V. Colares, S. Lima, N. Sousa et al., “Hydrogen peroxide-based products alter inﬂammatory and tissue damage-related proteins in the gingival crevicular ﬂuid of healthy volunteers: a randomized trial,” Scientiﬁc Reports, vol. 9, no. 1, p. 3457, 2019.

[35] N. Kamodyová, G. Minárík, J. Hodosy, and P. Celc, “Single consumption of Bryndza cheese temporarily affects oral microbiota and salivary markers of oxidative stress,” Current Microbiology, vol. 69, no. 5, pp. 716–724, 2014.

[36] M. Džunková, D. Martinez-Martinez, R. Gardlík et al., “Oxidative stress in the oral cavity is driven by individual-speciﬁc bacterial communities,” NPJ Biofilms and Microbiomes, vol. 4, no. 1, p. 29, 2018.

[37] J. Kreth, Y. Zhang, and M. C. Herzberg, “Streptococcus antagonism in oral bioﬁlms: Streptococcus sanguinis and Streptococcus gordonii interference with Streptococcus mutans,” Journal of Bacteriology, vol. 190, no. 13, pp. 4632–4640, 2008.

[38] L. Gölz, S. Memmert, B. Rath-Deschner et al., “LPS from P. gingivalis and hypoxia increases oxidative stress in periodontal ligament ﬁbroblasts and contributes to periodontitis,” Mediators of Inﬂammation, vol. 2014, Article ID 986264, 2014.

[39] T. Kiyoshima, N. Enoki, I. Kobayashi et al., “Oxidative stress caused by a low concentration of hydrogen peroxide induces senescence-like changes in mouse gingival ﬁbroblasts,” International Journal of Molecular Medicine, vol. 30, no. 5, pp. 1007–1012, 2012.

[40] A. Gharbi, A. Hamila, A. Bouguezz et al., “Biochemical parameters and oxidative stress markers in Tunisian patients with periodontal disease,” BMC Oral Health, vol. 19, no. 1, p. 225, 2019.

[41] K. C. Srivastava and D. Shrivastava, “Analysis of plasma lipid peroxidation and antioxidant enzymes status in patients of oral leukoplakia: a case control study,” Journal of International Society of Preventive & Community Dentistry, vol. 6, Suppl 3, pp. S213–S218, 2016.

[42] N. Okahashi, T. Sumitomo, M. Nakata, A. Sakurai, H. Kuwata, and S. Kawabata, “Hydrogen peroxide contributes to the epithelial cell death induced by the oral mitsu group of streptococci,” PLoS One, vol. 9, no. 1, article e86713, 2014.

[43] N. Okahashi, M. Nakata, T. Sumitomo, Y. Terao, and S. Kawabata, “Hydrogen peroxide produced by oral Streptococci induces macrophage cell death,” PLoS One, vol. 8, no. 5, article e62563, 2013.

[44] B. Calenic, K. Yaegaki, T. Murata et al., “Oral malodorous compound triggers mitochondrial-dependent apoptosis and causes genomic DNA damage in human gingival epithelial cells,” Journal of Periodontal Research, vol. 45, no. 1, pp. 31–37, 2010.

[45] B. Calenic, K. Yaegaki, A. Kozhuharova, and T. Imai, “Oral malodorous compound causes oxidative stress and p53-mediated programmed cell death in keratinocyte stem cells,” Journal of Periodontology, vol. 81, no. 9, pp. 1317–1323, 2010.

[46] T. Toliver-Kinsky, W. Cui, G. Törö et al., “H2S, a bacterial defense mechanism against the host immune response,” Infection and Immunity, vol. 87, p. e00272-18, 2019.

[47] K. Shatalin, E. Shatalina, A. Mironov, and E. Nudler, “H2S: a universal defense against antibiotics in bacteria,” Science, vol. 334, no. 6058, pp. 986–990, 2011.

[48] S. Y. Ng, K. X. Ong, S. T. Surendran et al., “Hydrogen sulﬁde sensitizes Acinetobacter baumannii to killing by antibiotics,” Frontiers in Microbiology, vol. 11, p. 1875, 2020.

[49] J. H. Zhang, Z. Dong, and L. Chu, “Hydrogen sulﬁde induces apoptosis in human periodontium cells,” Journal of Periodontal Research, vol. 45, no. 1, pp. 71–78, 2010.

[50] T. Murata, K. Yaegaki, W. Qian et al., “Hydrogen sulﬁde induces apoptosis in epithelial cells derived from human gingiva,” Journal of Breath Research, vol. 2, no. 1, 2008.

[51] K. Yaegaki, B. Calenic, and T. Imai, “Induction of Apoptosis in Human Keratinocyte Stem Cells: The Role of Hydrogen Sulfide,” Stem Cells and Cancer Stem Cells, vol. 3, pp. 371–376, 2012.

[52] C. Kobayashi, K. Yaegaki, B. Calenic et al., “Hydrogen sulﬁde causes apoptosis in human pulp stem cells,” Journal of Endodontics, vol. 37, no. 4, pp. 479–484, 2011.

[53] M. Fujimura, B. Calenic, K. Yaegaki et al., “Oral malodorous compound activates mitochondrial pathway inducing apoptosis in human gingival ﬁbroblasts,” Clinical Oral Investigations, vol. 14, no. 4, pp. 367–373, 2010.

[54] I. Aoyama, B. Calenic, T. Imai, H. Li, and K. Yaegaki, “Oral malodorous compound causes caspase-8 and -9 mediated programmed cell death in osteoblasts,” Journal of Periodontal Research, vol. 47, no. 3, pp. 365–373, 2012.

[55] B. Calenic, K. Yaegaki, N. Ishkitiev, Y. Kumazawa, T. Imai, and T. Tanaka, “p53-pathway activity and apoptosis in hydrogen sulﬁde-exposed stem cells separated from human gingival epithelium,” Journal of Periodontal Research, vol. 48, no. 3, pp. 322–330, 2013.

[56] K. Yaegaki, W. Qian, T. Murata et al., “Oral malodorous compound causes apoptosis and genomic DNA damage in human gingival ﬁbroblasts,” Journal of Periodontal Research, vol. 43, no. 4, pp. 391–399, 2008.

[57] R. Yang, T. Yu, D. Liu, S. Shi, and Y. Zhou, “Hydrogen sulﬁde promotes immunomodulation of gingiva-derived mesenchymal stem cells via the Fas/FasL coupling pathway,” Stem Cell Research & Therapy, vol. 9, no. 1, p. 62, 2018.
Oxidative Medicine and Cellular Longevity

[58] T. White, Y. Alimova, V. Alves et al., “Oral commensal bacteria differentially modulate epithelial cell death,” *Archives of Oral Biology*, vol. 120, article 104926, 2020.

[59] Q. Li, J. Zhou, L. Lin, H. Zhao, L. Miao, and Y. Pan, “Porphyromonas gingivalis degrades integrin β1 and induces ALF-mediated apoptosis of epithelial cells,” *Infectious Diseases*, vol. 51, no. 11-12, pp. 793–801, 2019.

[60] T. Desta and D. T. Graves, “Fibroblast apoptosis induced by Porphyromonas gingivalis is stimulated by a gingipain and caspase-independent pathway that involves apoptosis-inducing factor,” *Cellular Microbiology*, vol. 9, no. 11, pp. 2667–2675, 2007.

[61] S. M. Sheets, J. Potempa, J. Travis, C. A. Casiano, and H. M. Fletcher, “Gingipains from Porphyromonas gingivalis W83 induce cell adhesion molecule cleavage and apoptosis in endothelial cells,” *Infection and Immunity*, vol. 73, no. 3, pp. 1543–1552, 2005.

[62] A. P. Ribeiro-Sobrinho, F. Rabelo, C. B. Figueiredo et al., “Bacteria recovered from dental pulp induce apoptosis of lymph node cells,” *Journal of Medical Microbiology*, vol. 54, no. 4, pp. 413–416, 2005.

[63] W. Kang, Z. Jia, D. Tang et al., “Fusobacterium nucleatum facilitates apoptosis, ROS generation, and inflammatory cytokine production by activating Akt/MAPK and NF-κB signaling pathways in human gingival fibroblasts,” *Oxidative Medicine and Cellular Longevity*, vol. 2019, 2019.

[64] L. Tomasello, R. Mauceri, A. Coppola et al., “Mesenchymal stem cells derived from inflamed dental pulp and gingival tissue: a potential application for bone formation,” *Stem Cell Research & Therapy*, vol. 8, no. 1, p. 179, 2017.

[65] L. N. Zhou, C. S. Bi, L. N. Gao, Y. An, F. Chen, and F. M. Chen, “Macrophage polarization in human gingival tissue in response to periodontal disease,” *Oral Diseases*, vol. 25, no. 1, pp. 265–273, 2019.

[66] L. P. Menzel, W. Ruddick, M. H. Chowdhury et al., “Activation of vitamin D in the gingival epithelium and its role in gingival inflammation and alveolar bone loss,” *Journal of Periodontal Research*, vol. 54, no. 4, pp. 444–452, 2019.

[67] T. Ara, K. Kurata, K. Hirai et al., “Human gingival fibroblasts are critical in sustaining inflammation in periodontal disease,” *Journal of Periodontal Research*, vol. 44, no. 1, pp. 21–27, 2009.

[68] P. L. Wang, Y. Azuma, M. Shinohara, and K. Ohura, “Toll-like Receptor 4-Mediated Signal Pathway Induced by Porphyromonas gingivalis Lipopolysaccharide in Human Gingival Fibroblasts,” *Biochemical and Biophysical Research Communications*, vol. 273, no. 3, pp. 1161–1167, 2000.

[69] S. Nakamura, K. Shioya, B. Y. Hiraoka et al., “Porphyromonas gingivalis hydrogen sulfide enhances methyl mercaptan-induced pathogenicity in mouse abscess formation,” *Microbiology*, vol. 164, no. 4, pp. 529–539, 2018.

[70] I. K. Sundar, F. Javed, G. E. Romanos, and I. Rahman, “E-cigarettes and flavorings induce inflammatory and pro-senescence responses in oral epithelial cells and periodontal fibroblasts,” *Oncotarget*, vol. 7, no. 47, pp. 77196–77204, 2016.

[71] A. V. Pachevska, Y. V. Filimonov, V. Y. Filimonov et al., “Clinical and laboratory assessment the levels of oral hygiene, total protein, hydrogen sulfide and nitrogen metabolites in oral fluid in the development of inflammatory complications during orthodontic treatment of children,” *Wiadomosci Lekarskie*, vol. 72, no. 5, pp. 744–747, 2019.

[72] T. White, Y. Alimova, V. Alves et al., “Fibroblast apoptosis induced by Porphyromonas gingivalis is stimulated by a gingipain and caspase-independent pathway that involves apoptosis-inducing factor,” *Cellular Microbiology*, vol. 9, no. 11, pp. 2667–2675, 2007.

[73] S. M. Sheets, J. Potempa, J. Travis, C. A. Casiano, and H. M. Fletcher, “Gingipains from Porphyromonas gingivalis W83 induce cell adhesion molecule cleavage and apoptosis in endothelial cells,” *Infection and Immunity*, vol. 73, no. 3, pp. 1543–1552, 2005.

[74] A. P. Ribeiro-Sobrinho, F. Rabelo, C. B. Figueiredo et al., “Bacteria recovered from dental pulp induce apoptosis of lymph node cells,” *Journal of Medical Microbiology*, vol. 54, no. 4, pp. 413–416, 2005.

[75] W. Kang, Z. Jia, D. Tang et al., “Fusobacterium nucleatum facilitates apoptosis, ROS generation, and inflammatory cytokine production by activating Akt/MAPK and NF-κB signaling pathways in human gingival fibroblasts,” *Oxidative Medicine and Cellular Longevity*, vol. 2019, 2019.

[76] L. Tomasello, R. Mauceri, A. Coppola et al., “Mesenchymal stem cells derived from inflamed dental pulp and gingival tissue: a potential application for bone formation,” *Stem Cell Research & Therapy*, vol. 8, no. 1, p. 179, 2017.

[77] L. N. Zhou, C. S. Bi, L. N. Gao, Y. An, F. Chen, and F. M. Chen, “Macrophage polarization in human gingival tissue in response to periodontal disease,” *Oral Diseases*, vol. 25, no. 1, pp. 265–273, 2019.

[78] L. P. Menzel, W. Ruddick, M. H. Chowdhury et al., “Activation of vitamin D in the gingival epithelium and its role in gingival inflammation and alveolar bone loss,” *Journal of Periodontal Research*, vol. 54, no. 4, pp. 444–452, 2019.

[79] T. Ara, K. Kurata, K. Hirai et al., “Human gingival fibroblasts are critical in sustaining inflammation in periodontal disease,” *Journal of Periodontal Research*, vol. 44, no. 1, pp. 21–27, 2009.

[80] P. L. Wang, Y. Azuma, M. Shinohara, and K. Ohura, “Toll-like Receptor 4-Mediated Signal Pathway Induced by Porphyromonas gingivalis Lipopolysaccharide in Human Gingival Fibroblasts,” *Biochemical and Biophysical Research Communications*, vol. 273, no. 3, pp. 1161–1167, 2000.

[81] S. Nakamura, K. Shioya, B. Y. Hiraoka et al., “Porphyromonas gingivalis hydrogen sulfide enhances methyl mercaptan-induced pathogenicity in mouse abscess formation,” *Microbiology*, vol. 164, no. 4, pp. 529–539, 2018.

[82] I. K. Sundar, F. Javed, G. E. Romanos, and I. Rahman, “E-cigarettes and flavorings induce inflammatory and pro-senescence responses in oral epithelial cells and periodontal fibroblasts,” *Oncotarget*, vol. 7, no. 47, pp. 77196–77204, 2016.
and Porphyromonas gingivalis are associated with severity of periodontal tissue destruction,” *Journal of Periodontology*, vol. 72, no. 10, pp. 1354–1363, 2001.

[87] H. Y. Wang, L. Lin, W. Fu et al., “Preventive effects of the novel antimicrobial peptide Nal-P-113 in a rat periodontitis model by limiting the growth of Porphyromonas gingivalis and modulating IL-1β and TNF-α production,” *BMC Complementary and Alternative Medicine*, vol. 17, no. 1, p. 426, 2017.

[88] A. Oliveira, F. O. Costa, L. Nogueira et al., “Azithromycin and full-mouth scaling for the treatment of generalized stage III and IV periodontitis: a 6-month randomized comparative clinical trial,” *Brazilian Dental Journal*, vol. 30, no. 5, pp. 429–436, 2019.

[89] C. M. da Silva-Boghossian, R. M. do Souto, R. R. Luiz, and A. P. V. Colombo, “Association of red complex, *A. actinomyctetomitis* and non-oral bacteria with periodontal diseases,” *Archives of Oral Biology*, vol. 56, no. 9, pp. 899–906, 2011.

[90] J. Caroline, Y. Soeroso, H. Sunarto, B. M. Bachtiar, and B. Sulijaya, “Correlations between hydrogen sulfide and methyl mercaptan levels and the proportion of Porphyromonas gingivalis in patients with periodontitis,” *Journal of International Dental & Medical Research*, vol. 13, pp. 1359–1364, 2020.

[91] U. Kandalam, N. Ledra, H. Laubach, and K. V. Venkatachalam, “Inhibition of methionine gamma lyase deaminase and the growth of *Porphyromonas gingivalis*: A therapeutic target for halitosis/periodontitis,” *Archives of Oral Biology*, vol. 90, pp. 27–32, 2018.

[92] D. Stanisic, A. K. George, I. Smolenkova, M. Singh, and S. C. Tyagi, “Hyperhomocysteinemia: an instigating factor for periodontal disease,” *Canadian Journal of Physiology and Pharmacology*, vol. 99, no. 1, pp. 115–123, 2021.

[93] K. Ni and Y. Hua, “Hydrogen sulfide exacerbated periodontal inflammation and induced autophagy in experimental periodontitis,” *International Immunopharmacology*, vol. 93, article 107399, 2021.

[94] E. Guagliardo, R. Fusco, R. D’Amico et al., “Anti-inflammatory effect of ATB-352, a H2S–releasing ketoprofen derivative, on lipopolysaccharide-induced periodontitis in rats,” *Pharmacological Research*, vol. 132, pp. 220–231, 2018.

[95] B. S. Herrera, L. S. Coimbra, A. R. da Silva et al., “The H2S-releasing naproxen derivative, ATB-346, inhibits alveolar bone loss and inflammation in rats with ligature-induced periodontitis,” *Medical Gas Research*, vol. 5, no. 1, p. 4, 2015.

[96] H. Toker, H. Balci Yuce, F. Goze, H. Ozcemir, A. Akpinar, and V. Bostanci, “The effects of hydrogen sulfide on alveolar bone loss in periodontitis,” *Minera Stomatologica*, vol. 63, no. 4, pp. 103–110, 2014.

[97] A. J. Niederauer, R. A. Guimarães, K. L. Oliveira et al., “H<sub>2</sub>S replenishment in periodontal immune-inflammatory response and bone loss: a study in rats,” *Acta Odontologica Latinoamericana*, vol. 32, no. 3, pp. 164–171, 2019.

[98] S. Patel and N. Saberi, “The ins and outs of root resorption,” *British Dental Journal*, vol. 224, no. 9, pp. 691–699, 2018.

[99] Z. Fuss, I. Tsesis, and S. Lin, “Root resorption–diagnosis, classification and treatment choices based on stimulation factors,” *Dental Traumatology*, vol. 19, no. 4, pp. 175–182, 2003.

[100] G. Gay, S. Ravera, T. Castrofriolo et al., “Root resorption during orthodontic treatment with Invisible®: a radiometric study,” *Progress in Orthodontics*, vol. 18, no. 1, p. 12, 2017.

[101] C. Lu, L. Chen, and Y. Hua, “Cystathionine gamma lyase aggravates orthodontic root resorption in mice,” *Annals of Translational Medicine*, vol. 7, no. 23, p. 787, 2019.

[102] Y. Hu, W. Liu, Z. Liu, W. Kuang, and H. He, “Receptor activator of nuclear factor-kappa ligand, OPG, and IGFl-expression during orthodontically induced inflammatory root resorption in the recombinant human growth hormone-treated rats,” *The Angle Orthodontist*, vol. 85, no. 4, pp. 562–569, 2015.

[103] R. C. Page, “Gingivitis,” *Journal of Clinical Periodontology*, vol. 13, no. 5, pp. 345–355, 1986.

[104] P. Holm-Pedersen, N. Agerbaek, and E. Theilade, “Experimental gingivitis in young and elderly individuals,” *Journal of Clinical Periodontology*, vol. 2, no. 1, pp. 14–24, 1975.

[105] P. R. Hennet, B. Delille, and J. L. Davot, “Oral malodor measurements on a tooth surface of dogs with gingivitis,” *American Journal of Veterinary Research*, vol. 59, no. 3, pp. 255–257, 1998.

[106] A. Pavolotskaya, G. McCombs, M. Darby, K. Marinak, and N. N. Dayanand, “Sulcular sulfide monitoring: an indicator of early dental plaque-induced gingival disease,” *Journal of Dental Hygiene*, vol. 80, no. 1, p. 11, 2006.

[107] H. Zhou, G. B. McCombs, M. L. Darby, and K. Marinak, “Sulphur by-product: the relationship between volatile sulphur compounds and dental plaque-induced gingivitis,” *The Journal of Contemporary Dental Practice*, vol. 5, no. 2, pp. 27–39, 2004.

[108] H. Sung, J. Ferlay, R. L. Siegel et al., “Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries,” *CA: A Cancer Journal for Clinicians*, vol. 71, pp. 209–249, 2021.

[109] H. Zhou, G. B. McCombs, M. L. Darby, and K. Marinak, “Sulphur by-product: the relationship between volatile sulphur compounds and dental plaque-induced gingivitis,” *The Journal of Contemporary Dental Practice*, vol. 5, no. 2, pp. 27–39, 2004.

[110] A. Capote-Moreno, P. Brabyn, M. F. Muñoz-Guerra et al., “Oral squamous cell carcinoma: epidemiological study and risk factor assessment based on a 39-year series,” *International Journal of Oral and Maxillofacial Surgery*, vol. 49, no. 12, pp. 1525–1534, 2020.

[111] I. Ganly, L. Yang, R. A. Giese et al., “Periodontal pathogens are a risk factor of oral cavity squamous cell carcinoma, independent of tobacco and alcohol and human papillomavirus,” *International Journal of Cancer*, vol. 145, no. 3, pp. 775–784, 2019.

[112] N. Al-Hebsi, A. T. Nasher, M. Y. Maryoud et al., “Inflammatory bacteriome featuring Fusobacterium nucleatum and _Pseudomonas aeruginosa_ identified in association with oral squamous cell carcinoma,” *Scientific Reports*, vol. 7, no. 1, p. 1834, 2017.

[113] M. Perera, N. N. Al-Hebsi, I. Perera et al., “Inflammatory bacteriome and oral squamous cell carcinoma,” *Journal of Dental Research*, vol. 97, no. 6, pp. 752–753, 2018.

[114] C. Y. Yang, Y. M. Yeh, H. Y. Yu et al., “Oral microbiota community dynamics associated with oral squamous cell carcinoma staging,” *Frontiers in Microbiology*, vol. 9, p. 862, 2018.

[115] L. Wen, W. Mu, H. Lu et al., “Porphyromonas gingivalis promotes oral squamous cell carcinoma progression in an
immune microenvironment,” *Journal of Dental Research*, vol. 99, no. 6, pp. 666–675, 2020.

[116] F. Geng, Y. Zhang, Z. Lu, S. Zhang, and Y. Pan, “Fusobacte-
rium nucleatumCaused DNA damage and promoted cell prolif-
eration by theKu70/p53Pathway in oral cancer cells,” *DNA
and Cell Biology*, vol. 39, no. 1, pp. 144–151, 2020.

[117] A. T. Meram, J. Chen, S. Patel et al., “Hydrogen sulfide is
increased in oral squamous cell carcinoma compared to adja-
cent benign oral mucosae,” *Anticancer Research*, vol. 38, 
no. 7, pp. 3843–3852, 2018.

[118] J. Drain and M. O. Fleming, “Palliative management of mal-
odorous squamous cell carcinoma of the oral cavity with
Manuka honey,” *Journal of Wound, Ostomy, and Continence
Nursing: official publication of The Wound, Ostomy and Con-
tinence Nurses Society*, vol. 42, no. 2, pp. 190–192, 2015.

[119] R. van de Goor, J. Hardy, M. van Hooren, B. Kremer, and
K. W. Kross, “Detecting recurrent head and neck cancer using
electronic nose technology: a feasibility study,” *Head &
Neck*, vol. 41, no. 9, pp. 2983–2990, 2019.

[120] S. Hartwig, J. D. Raguse, D. Pfiitzner, R. Preissner et al., “Volatile organic compounds in the breath of oral squamous cell carcinoma patients: a pilot study,” *Oto-
laryngology–Head & Neck Surgery: official journal of American
Academy of Otolaryngology-Head and Neck Surgery*, vol. 157, no. 6, pp. 981–987, 2017.

[121] Z. Ma, Q. Bi, and Y. Wang, “Hydrogen sulfide accelerates cell
cycle progression in oral squamous cell carcinoma cell lines,” 
*Oral Diseases*, vol. 21, no. 2, pp. 156–162, 2015.

[122] S. Zhang, H. Bian, X. Li et al., “Hydrogen sulfide promotes
cell proliferation of oral cancer through activation of the
COX2/AKT/ERK1/2 axis,” *Oncology Reports*, vol. 35, no. 5, 
pp. 2825–2832, 2016.

[123] T. Hoppe, D. Kraus, N. Novak et al., “Oral pathogens change
proliferation properties of oral tumor cells by affecting gene
expression of human defensins,” *Tumour Biology: the journal of the International Society for Oncodevelopmental Biology and Medicine*, vol. 37, no. 10, pp. 13789–13798, 2016.

[124] C. L. Ellington, M. Goodman, S. A. Kono et al., “Adenoid cysti-
carcinoma of the head and neck,” *Cancer*, vol. 118, no. 18, 
pp. 4444–4451, 2012.

[125] J. P. Bonaparte, R. Hart, J. Trits, and M. S. Taylor, “Incidence of adenoid cystic carcinoma in Nova Scotia: 30-year population-based epidemiologic study,” *Journal of Otolaryng-
ology - Head & Neck Surgery = Le Journal d’oto-rhino-laryngo-
logie et de chirurgie cervico-faciale*, vol. 37, pp. 642–648, 2008.

[126] R. E. Friedrich and V. Bleckmann, “Adenoid cystic carcinoma of
salivary and lacrimal gland origin: localization, classification, 
clinical pathological correlation, treatment results and
long-term follow-up control in 84 patients,” *Anticancer Research*, vol. 23, no. 2A, pp. 931–940, 2003.

[127] X. Liu, Q. F. Yang, N. Gan, and D. Q. Yang, “Oral microbio-
logical diversity in patients with salivary adenoid cystic carci-
noma,” *West China Journal of Stomatology*, vol. 37, no. 3, 
pp. 304–308, 2019.

[128] K. Dongsoo, J. Chen, E. Wei et al., “Hydrogen sulfide and
hydrogen sulfide-synthesizing enzymes are altered in a case of oral adenoid cystic carcinoma,” *Case Reports in Oncology*, vol. 11, no. 2, pp. 585–590, 2018.

[129] Y. Wang, S. Wang, and B. Zhang, “A population-based anal-
alysis of mucoepidermoid carcinoma of the oral cavity,” *The Laryngoscope*, vol. 131, no. 3, pp. E857–E863, 2021.

[130] K. Rajasekaran, V. Stubbs, J. Chen et al., “Mucoepidermoid
carcinoma of the parotid gland: a National Cancer Database
study,” *American Journal of Otolaryngology*, vol. 39, no. 3, 
pp. 321–326, 2018.

[131] D. Kim, J. Chen, A. Meram et al., “Hydrogen sulfide
synthesizing enzymes are altered in a case of oral cavity
mucoepidermoid carcinoma,” *Case Reports in Oncology*, vol. 11, no. 3, pp. 682–687, 2018.

[132] E. A. Ostrakhovitch, S. Akakura, R. Sanokawa-Akakura, 
S. Goodwin, and S. Tabibzadeh, “Dedifferentiation of cancer
cells following recovery from a potentially lethal damage is mediat-
ed by H3S-Nampt,” *Experimental Cell Research*, vol. 330, no. 1, pp. 135–150, 2015.

[133] J. You, X. Shi, H. Liang et al., “Cystathionine-γ-lyase pro-
motes process of breast cancer in association with STAT3 sig-
naling pathway,” *Oncotarget*, vol. 8, no. 39, pp. 65677–65686, 2017.

[134] E. A. Chybowski, G. N. Glickman, Y. Patel, A. Fleury, 
E. Solomon, and J. He, “Clinical outcome of non-surgical root
channel treatment using a single-cone technique with endose-
quence bioceramic sealer: a retrospective analysis,” *Journal of Endodontics*, vol. 44, no. 6, pp. 941–945, 2018.

[135] A. Riis, S. Tascheri, M. Del Fabbro, and T. Kvist, “Tooth sur-
vival after surgical or nonsurgical endodontic retreatment:
long-term follow-up of a randomized clinical trial,” *Journal of Endodontics*, vol. 44, no. 10, pp. 1480–1486, 2018.

[136] M. Yamaguchi, Y. Noiri, Y. Itoh et al., “Factors that cause
endodontic failures in general practices in Japan,” *BMC Oral
Health*, vol. 18, no. 1, p. 70, 2018.

[137] L. M. Lin, J. E. Skribner, and P. Gaengler, “Factors associated with endodontic treatment failures,” *Journal of Endodontics*, vol. 18, no. 12, pp. 625–627, 1992.

[138] G. Sundqvist, D. Figdor, S. Persson, and U. Sjögren, “Micro-
biologic analysis of teeth with failed endodontic treatment
and the outcome of conservative re-treatment,” *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and End-
dodontics*, vol. 85, no. 1, pp. 86–93, 1998.

[139] E. Jacobi-Gresser, S. Schütt, K. Huesker, and V. Von Baehr,
“Methyl mercaptan and hydrogen sulfide products stimulate
proinflammatory cytokines in patients with necrotic pulp tis-
sue and endodontically treated teeth,” *Journal of Biological
Regulators and Homeostatic Agents*, vol. 29, no. 1, pp. 73–
84, 2015.

[140] J. Lechner and V. von Baehr, “Stimulation of proinflamma-
tory cytokines by volatile sulfur compounds in endodonti-
cally treated teeth,” *International Journal of General
Medicine*, vol. 8, pp. 109–118, 2015.

[141] G. Oláh, K. Módis, G. Törö, M. R. Hellmich, B. Szczesny,
and Cell Biology of Cardiovascular Pharmacology and Therapeutics*, vol. 25, no. 5, pp. 472–483, 2020.

[142] K. Nguyen, V. Q. Chau, A. G. Mauro et al., “Hydrogen sulfide
therapy suppresses cfosflin-2 and attenuates ischemic heart
failure in a mouse model of myocardial infarction,” *Journal of Cardiovascular Pharmacology and Therapeutics*, vol. 25, 
no. 5, pp. 472–483, 2020.

[143] J. A. Mendes, M. C. Ribeiro, G. Reis Filho et al., “Hydrogen
sulfide inhibits apoptosis and protects the bronchial epithe-
lium in an allergic inflammation mice model,” *International Immunopharmacology*, vol. 73, pp. 435–441, 2019.
[144] L. Xie, Y. Gu, M. Wen et al., "Hydrogen sulfide induces Keap1 S-sulfhydration and suppresses diabetes-accelerated atherosclerosis via Nrf2 activation," *Diabetes*, vol. 65, no. 10, pp. 3171–3184, 2016.

[145] P. K. Sreenivasan and E. Gittins, "Effects of low dose chlorhexidine mouthrinses on oral bacteria and salivary microflora including those producing hydrogen sulfide," *Oral Microbiology and Immunology*, vol. 19, no. 5, pp. 309–313, 2004.

[146] M. I. Williams, J. Vazquez, and D. Cummins, "Clinical comparison of a new manual toothbrush on the level of hydrogen-sulfide-forming bacteria on the tongue," *Compendium of Continuing Education in Dentistry*, vol. 25, 10 Suppl 2, pp. 17–21, 2004.

[147] P. Sreenivasan, "The effects of a triclosan/copolymer dentifrice on oral bacteria including those producing hydrogen sulfide," *European Journal of Oral Sciences*, vol. 111, pp. 223–227, 2003.

[148] E. Van der Sluijs, D. E. Slot, E. W. Bakker, and G. A. Van der Weijden, "The effect of water on morning bad breath: a randomized clinical trial," *International Journal of Dental Hygiene*, vol. 14, no. 2, pp. 124–134, 2016.

[149] K. Iha, N. Suzuki, M. Yoneda, T. Takeshita, and T. Hirofuji, "Effect of mouth cleaning with hinokitiol-containing gel on oral malodor: a randomized, open-label pilot study," *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*, vol. 116, no. 4, pp. 433–439, 2013.

[150] K. Watanabe, H. Hiramine, T. Toyama, and N. Hamada, "Effects of French pine bark extract chewing gum on oral malodor and salivary bacteria," *Journal of Nutritional Science and Vitaminology*, vol. 64, no. 3, pp. 185–191, 2018.

[151] C. Kara, T. Demir, R. Orbak, and A. Tezel, "Effect of Nd: YAG laser irradiation on the treatment of oral malodour associated with chronic periodontitis," *International Dental Journal*, vol. 58, no. 3, pp. 151–158, 2008.

[152] G. R. Nogueira-Filho, P. M. Duarte, S. Toledo, C. P. Tabchoury, and J. A. Cury, "Effect of triclosan dentifrices on mouth volatile sulphur compounds and dental plaque trypsin-like activity during experimental gingivitis development," *Journal of Clinical Periodontology*, vol. 29, no. 12, pp. 1059–1064, 2002.

[153] B. Acar, E. Berker, Ç. Tan, Y. D. İlarslan, M. Tekçıçek, and İ. Tezcan, "Effects of oral prophylaxis including tongue cleaning on halitosis and gingival inflammation in gingivitis patients-a randomized controlled clinical trial," *Clinical Oral Investigations*, vol. 23, no. 4, pp. 1829–1836, 2019.