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***Helicobacter pylori* Infection and Halitosis – Evidence, Hypothesis, and Korean Red Ginseng to Mitigate Its Effect**

Kyu Hyun Han, Jong-Min Park, Young-Min Han, Joo Young Cho, Weon Jin Ko and Ki Baik Hahm

Additional information is available at the end of the chapter

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Abstract

Halitosis is a common and ignored condition, but in some, it is a disease-associated health problem, suggestive of overt disease conditions and has affected about 25–30% of world's population, bothering nonmedical social disturbance in many people. Although two kinds, pseudohalitosis and halitophobia, are also concerned, genuine halitosis originated from the oral cavity, such as gingivitis, caries, and poor oral hygiene, in 80% and the remaining 20% are extraoral sources of halitosis, which should not be ignored because of stigmata suggestive of overt tissue dysfunctions, for instance, poor nutrition and hygiene, alcohol abuse, smoking, and systemic illness such as chronic obstructive pulmonary disease, liver cirrhosis, diabetes mellitus, and chronic renal diseases. In this chapter, *Helicobacter pylori* (*H. pylori*)–associated halitosis as one of the extragastric manifestations is introduced. Since diagnostics of halitosis includes subjective methods (examiner's sense of smell) and objective methods (instrumental analysis), under the hypothesis of a possible relationship between *H. pylori* infection and objective halitosis, the real levels of volatile sulfur compounds (VSCs) in the breath showed significant correlation between VSC levels and the degree of *H. pylori*–associated erosive gastritis as well as gastric cancer. These findings are further validated through either measuring H₂S level in gastric juices of *H. pylori*–infected gastritis or checking the expressions of cystathionine-γ-lyase (CSE) and cystathionine-β-synthase (CBS) responsible for H₂S generation in biopsied stomach. The eradication of *H. pylori* significantly ameliorated halitosis, accompanied with significant reductions in gastric H₂S levels (p<0.01). Korean red ginseng was very effective in either reducing *H. pylori*–associated H₂S or alleviating halitosis in patients with *H. pylori*–associated chronic atrophic gastritis. Conclusively, *H. pylori* infection demonstrates to have an important relationship with the development of halitosis, and its eradication could possibly promote the improvement of this condition.

Keywords: Halitosis, *Helicobacter pylori*, volatile sulfur compounds, hydrogen sulfide, gastritis, gastroesophageal reflux disease

1. Introduction

1.1. Halitosis, pseudohalitosis, and halitophobia

Halitosis is a very common and unpleasant condition, affecting around 1/4–1/3 of the general population, which can be classified into the following three conditions, genuine halitosis, pseudohalitosis, and halitophobia based on their pathogenesis [1, 2]; genuine halitosis is usually related to an organic pathology, such as periodontitis, gingivitis, gastritis, and other systemic illness, and malodor molecules such as volatile sulfur compounds (VSCs) that arise usually from bacterial interactions generate the basis of oral malodor, such as hydrogen sulfide (H_2S), methyl mercaptan (CH_3SH), and dimethyl sulfide [$(\text{CH}_3)_2\text{S}$]. In addition, sulfur compounds, short-chain fatty acids, such as butyric acid ($\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$), propionic acid ($\text{CH}_3\text{CH}_2\text{COOH}$), and valeric acid ($\text{C}_5\text{H}_{10}\text{O}_2$), diamines, including cadaverine [$\text{NH}_2(\text{CH}_2)_5\text{HN}_2$] and putrescine [$\text{NH}_2(\text{CH}_2)_4\text{HN}_2$], 1-proxy-2-propanol, phenyl compounds, such as indole, skatole, phyridiene, alkalines, ketones, and nitrogen-containing compounds, such as urea [$(\text{NH}_2)_2\text{CO}_2$] and ammonia (NH_3), may contribute to malodor of halitosis [3, 4]. When the concentration of these molecules in halitotic breath exceeds a threshold detected by objective methods, genuine halitosis can be diagnosed. Furthermore, pathologies of the tongue, poor oral hygiene, deep caries, and postnasal drainage are primarily associated with halitosis, in which condition, species such as *Peptostreptococcus anaerobius*, *Bacteriodes* spp., *Centipedia peritontii*, *Eubacterium* spp., *Topbium parvulum*, *Camplyobacter rectus*, *Eikenella corrodens*, *Eubacterium sulci*, *Fusobacterium nucleatum* or *periodonticum*, *Porphyromonas endodontalis* or *gingivalis*, *Solobacterium moorei*, *Bacteriodes forsythus*, *Treponema denticola*, and *Streptococcus salivariou* are well-known bacterial strains responsible for halitosis [5, 6]. Next, pseudohalitosis can be described as a situation where obvious malodor is not perceived by others, but only perceived by the patient, that is, patients who consider to have bad breath, but who does never been acknowledged by others, the patients with pseudo-halitosis often coinciding with depression and anxiety [7]. Finally, halitophobia is a situation when a patient complains about halitosis after the treatment of either genuine halitosis or pseudo-halitosis, even though no objective clues were documented. Therefore, patients with halitophobia are usually accompanied with vague psychiatric disturbance [2]. Although 0.5–1% of the adult population is affected with halitophobia during their social life, most patients with halitophobia frequently hop and hop from clinic/specialist to clinic/specialist in order to find an argument for their self-esteemed problem [8].

Halitosis relevant with practical clinical problems can be classified into the following two clinical situations according to origin, one is oral halitosis, around 90% in all, and the other is extraoral halitosis, remaining 10% among whole halitosis [9]. Since VSCs are responsible for halitosis irrespective of origin, in case of extraoral halitosis, VSCs generally generated from the body, travel to the lung through the vascular system, and pull out through breath from the alveoli. As another systemic diseases causing extraoral halitosis, liver disease, such as cirrhosis, hepatoma, and hepatic failure, uremia from end-stage renal disease, and

metabolic disorder, such as diabetic ketoacidosis and other kinds of metabolic disorders had been reported. Also, excess food intake (food factors) like garlic or onion can be common etiology for halitosis [10, 11]. Among these system diseases, it must be kept in mind that halitosis can be a clue symptom suggestive of serious cancers, especially gastric, liver, and pancreatic cancer. Furthermore, halitosis can be one of the prominent extragastric manifestations suggestive of *Helicobacter pylori* (*H. pylori*)–associated ulcer or cancer because of the evidence showing correlation between VSCs levels and these gastric lesions [12, 13], about which detailed description will be followed. As nonoral cause of halitosis, sinusitis, tonsillitis, bronchiectasis, subphrenic abscess, esophageal diverticulum, pyloric stenosis, gastroesophageal reflux disease (GERD), and hepatitis are very common diseases relevant to halitosis encountered in clinic.

2. Halitosis provoked by gastrointestinal (GI) diseases

Apart from oral cavity, the GI tract diseases caused halitosis as presenting symptoms, though physician and patients still abusively believe that halitosis originates from the oral cavity or stomach. For instance, almost all patients suffering from some erosive changes in esophago-gastric organ, halitosis might be very common and earliest manifestation. In our earlier investigation [15], almost all patients with GERD or some degree of erosive gastritis, real levels of VSCs were significantly increased. Other examples of clinical diseases, such as pyloric stenosis, duodenal obstruction, aorto-enteric anastomosis, pharyngeal pouches, Zenker's diverticulum, and hiatal hernia, usually led to halitosis as usual clinical manifestations. Especially, GERD, achalasia, or other malabsorption syndromes may cause halitosis accompanied with other symptoms of retching and flatulence. In cases of intestinal obstruction, halitosis may be detectable because the first sign noticed to either patient's relatives or physician. Halitosis is usually noted after consuming dietary products, such as garlic, onions, and some spiced foods cause transient unpleasant odor or halitosis [14]. Yoo *et al.* [15] found that erosive changes in the esophago-gastro-duodenal mucosa were significantly correlated with increased levels of VSCs, suggesting that halitosis could be a symptom suggestive of the erosive diseases of the upper gut mucosa. In detail, as shown in Figure 1, erosive changes in the esophageal mucosa, erosive type GERD, were strongly associated with VSC levels, ascertaining the hypothesis that halitosis can be a potential biomarker for the discrimination between erosive GERD and nonerosive GERD, assuring the presence of erosive change in the lower EG junction [16]. In summary, GI pathology was very common in patients with halitosis as extraoral origin [17], approximately 50–60% among all gastroenterology patients. Conclusively, halitosis symptom, usually ignored as insignificant, should be investigated to search for etiology even in nondental area. Accompanied with halitosis, there has been a report [18] describing that *H. pylori* colonization of tongue mucosa increased incidence of atrophic glossitis and burning mouth syndrome, especially accompanied with halitosis.

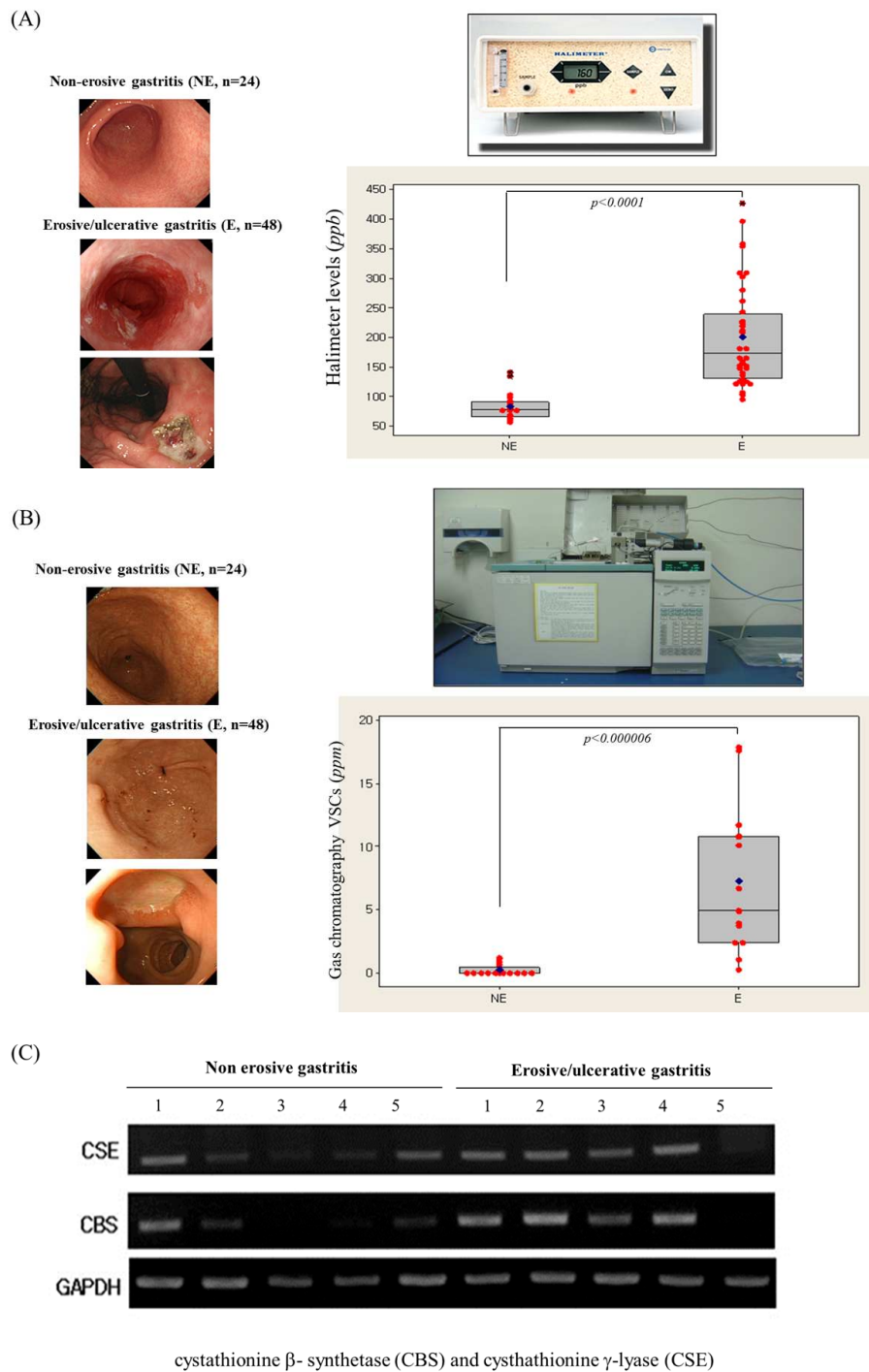


Figure 1. Correlation between EG lesion and halitosis. (A) Halitosis measurement with Halimeter in 72 patients with halitosis. Significant differences in Halimeter ppb were noted between patients with superficial gastritis and patients with erosive/ulcerative lesion ($p < 0.0001$) (B) halitosis measurement with gas chromatography (GC) in same 72 patients with halitosis. Significant differences in VSCs ppm were noted between patients with superficial gastritis and patients with erosive/ulcerative lesion ($p < 0.000006$). (C) The expressions of CSE and CBA according to EG mucosal changes. The mean expressions of CBS or CSE were significantly increasingly noted in patients with erosive changes. All of these results consistently suggested “halitosis” as possible biomarker predicting the presence of mucosal destruction and resulting putrefactive process in stomach.

3. Hydrogen sulfide (H₂S) biogas: Good, bad, ugly in its biology, and halitosis

Although biologic gas such as H₂S as principal gas molecule is responsible for causing halitosis, there are contradictory biological implications of three major biogas, nitric oxide (NO), H₂S, and carbon monoxide (CO), in anti-inflammatory substances, promoting resolution of inflammatory processes, imposing several situations, including ischemic-reperfusion injury, cardioprotection, sepsis, hemostasis, fibrosis, pancreatitis, separately, but sometimes interacting each other [19, 20]. Interestingly, H₂S stands for dual functions, inflammatory mediator or anti-inflammatory mediator [21], gaseous intracellular transducer implicated in either abnormal pathology or normal physiology [22], positioning homeostasis as friend or foe [23]. H₂S and their responsible enzymes, cystathionine- β -synthase (CBS) and cystathionine- γ -lyase (CSE), played good or bad, but ugly biological implications dependent on cellular context and disease conditions.

Though many new technologies to detect endogenous H₂S production and to develop novel H₂S-delivery compounds have been invented [24], simple gas with complex biology of good, bad, and ugly aspect, in this chapter, the way to detect VSCs, the implication of H₂S among VSCs, and their regulations will be introduced. The Halimeter (Interscan corporation, Chatsworth, CA, Figure 1A) and OralChroma (Abimedical corporation, Kanagawa, Japan) are electronic devices available to detect some of the VSCs in expired air easily in clinic. These two devices are a portable gas chromatograph featuring easy to handle, lower cost, higher performance, time saving, fast results, very accurate, and reproducible even compared with conventional gas chromatographs. However, the limitation is that they limitedly target three gases: H₂S, CH₃SH, and (CH₃)₂S. With the Halimeter measurement, the total amount of VSCs in *parts per billion* (ppb) in breathing air is shown. In normal situations, this value is less than 100 ppb. When 300–400 ppb are detected in the mouth air, objective halitosis can be confirmed, of course, the changes of ppb level can be traced after some interventions to mitigate halitosis [25]. Though they are rather inexpensive and can be controlled by untrained staff, the limited diversity in the explored gasses and inconvenience by examiner's cooperation should be further improved. On the other hand, the OralChroma may produce a more comprehensive assessment of VSCs production by oral microflora compared to Halimeter [26]. Of course, gas chromatography (GC) analysis can be performed on diverse sources, such as saliva, tongue debris, aspirated gastric juices, and even biopsied tissues, in addition to breath and almost all different air components can be detected, golden standard for halitosis, but not easy to measure and expensive [27]. In expired air, almost 500 different substances can be measured with GC (Figure 1B). Although GC has been used since the late 1960s, GC is still in an experimental stage, infrequent use for clinic [28]. Though GC has several advantages, such as an analysis of almost all components, high sensitivity, specificity, and noninvasive, it is very expensive, hard to handle because a well-trained staff is mandatory and not portably used [29]. Besides of these measurements, the scientific and practical value of additional or alternative measurement methods, such as benzoyl-DL-arginine-naphthylamide (BANA) test, chemical sensors,

salivary incubation test, quantifying galactosidase activity, ammonia monitoring, Ninhydrin method, and PCR, has been applied in clinic.

3.1. H₂S as dual-edged sword, is it neurotransmitter or inflammatory mediator?

H₂S is a well-known toxic gas that is synthesized from the amino acids, cysteine and homocysteine, by two enzymes, CBS and CSE [30, Figure 1C]. Like other biogas, CO or NO, H₂S is a signaling molecule implicated in either physiological actions of the cardiovascular or digestive system or pathophysiological actions in homeostasis, proliferation, and apoptosis of vascular smooth muscle cells, insulin release, nociceptive effects, cytoprotection, but contradictory action of inflammatory mediators, for instance, pancreatitis, chronic obstructive pulmonary disease, joint inflammation, sepsis, and *H. pylori*-associated gastritis in gastroenterology [23, 31–33]. In detail, in pancreatitis, especially in a form of severe acute pancreatitis (SAP), the fact that treatment with DL-propargylglycine (PAG) induced pancreatic acinar cell apoptosis and decreased the pathological scores as well as inflammatory parameters, whereas administration of NaHS significantly aggravated SAP suggested the implication of H₂S in pancreatitis [34]. For instance, Bhatia M *et al.* [35] published that proinflammatory role of H₂S regulated the severity of pancreatitis and even associated lung injury. On the other hand, in endotoxemia or sepsis model, H₂S contributed to recovery or rescuing actions [36–38].

4. Halitosis as one of extragastric manifestations of *H. pylori* infection (Figure 3)

H. pylori was shown to produce H₂S and CH₃SH, major oral malodor, inducing VSCs, suggesting that *H. pylori* can contribute to the development of halitosis relevant with tissue destruction in the GI tract [12]. The findings that as *H. pylori*-associated chronic gastritis worsened, it caused significant increase in levels of VSCs, but significant improvement of halitosis after eradication signified that halitosis can be overtly correlated with extra-gastric symptoms of *H. pylori* infection. Taken together with the additional fact that *H. pylori* infection was responsible for diverse oral pathologies [39], there are two liaisons between *H. pylori* infection and halitosis, one is that *H. pylori* can provoke halitosis through oral cavity infection [40] and the other is that gastric pathologies caused by chronic *H. pylori* infection are responsible for halitosis as extragastric manifestation [41]. According to literature search, there were 48 articles reporting the association between saliva/plaque and *H. pylori* infection. As example showing association between *H. pylori* infection and various oral diseases, Tiomny *et al.* [42] reported that in Israel, when studied six patients with halitosis and five of whom were *H. pylori* positive, the symptoms of halitosis disappeared after successful eradication. Similar results were reported by Ierardi *et al.* [43] documented with real measurement of VSC in *H. pylori* infection. Serin *et al.* [44] administered triple eradication therapy to subjects with *H. pylori*-positive halitosis and found about two third of patients were free from halitosis, all of these studies consistently signified that halitosis is a frequent and treatable symptom in *H. pylori*-positive chronic gastritis and can be a valid indication for *H. pylori* eradication. Our

group extended these investigations, in which any erosive or ulcerative lesions relevant with *H. pylori* infection provoked higher rate of halitosis and healing from erosive changes warranted improvement of halitosis in all subjects, in this study objective measurements as well as subjective changes of halitosis were done with real value of H₂S measured by either gas chromatography or Halimeter. Recently, it was reported that *H. pylori* infection increased the risk of BHH (burning, halitosis, and lingual dorsum hyperplasia). *H. pylori* detection in the oral cavity by histopathologic diagnosis and molecular biology was confirmed in 87% patients with BHH, but only lesser than 2.6% in other kinds of oral diseases [39,45].

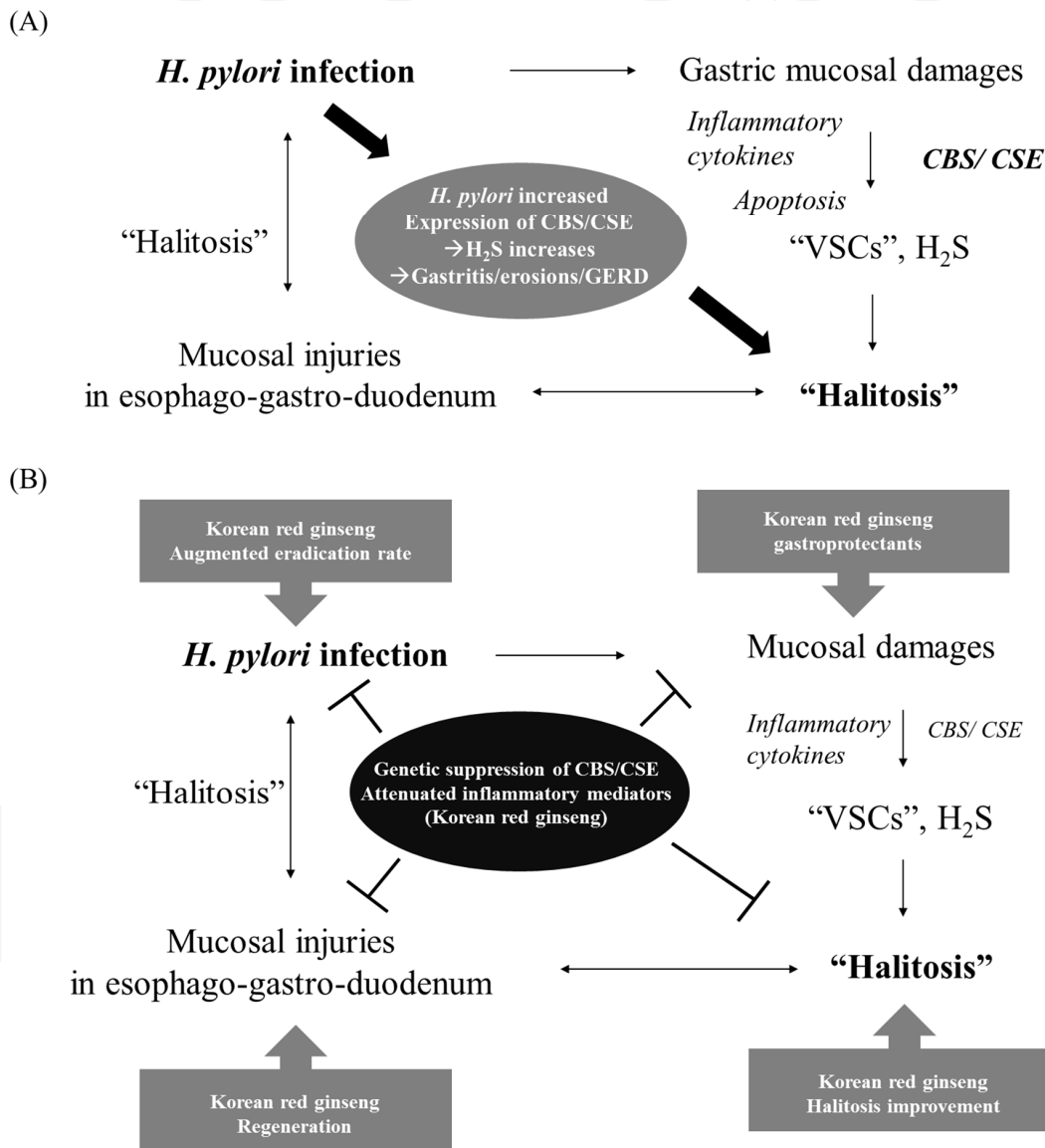


Figure 2. Halitosis as possible extragastric manifestation of *H. pylori* infection and relief with KRG. (A) *H. pylori* infection led to several pathogenic changes in gastric mucosa, oxidative stress, inflammatory mediators, apoptosis, and increasing expression of CBS and CSE, after which increased H₂S seems to be responsible for inflammatory, ulcerative, and halitosis changes. (B) KRG was identified as natural product controlling CBS or CSE expressions followed with additional action mechanisms of augmenting eradication, lessening gastric inflammation, and ameliorating halitosis.

There were two translational studies confirming the association between *H. pylori* infection and halitosis through real measurements of VSCs in clinical setting: one was the study by Suzuki *et al.* [46] that used saliva from the 25 halitosis patients associated with *H. pylori* infection; the clinical symptoms associated with halitosis and periodontal symptoms were significantly greater in the *H. pylori*-positive subjects and the other from our author's group [15] shows that halitosis could be an effective biomarker in predicting *H. pylori*-associated erosive and inflammatory changes, of which were significantly correlated with halitosis improvement after eradication. Reports regarding the long-term outcome that eradication of *H. pylori* in patients with functional dyspepsia warranted sustained improvement of halitosis were available [47] and they strongly supported the existence of a close link between *H. pylori* infection and halitosis. Conclusively *H. pylori* eradication should be considered in patients with troublesome halitosis, bothering patients with limited social activities due to halitosis (Figure 2A).

5. Amelioration of troublesome halitosis through suppressing *H. pylori*-associated H₂S with natural products

Lee *et al* [41] investigated 88 patients with functional dyspepsia presenting with halitosis, all of them showed very high levels of Halimeter >100 ppb, on whom tests were repeated after 10 weeks of Korean red ginseng (KRG) administration. As results, most patients with successful eradication of *H. pylori* benefited with subjective and objective improvement of halitosis. Before the current clinical trials, positive outcomes were anticipated in *in vitro* investigation that KRG extracts significantly decreased *H. pylori*- or NaHS-induced CSE expressions concomitant with attenuated levels of H₂S, IL-6, IL-8, as well as IL-1 β mRNA. The findings that more than half of the cases (52.3–65.0%) became free of halitosis with KRG treatment alone, but it was the combination of a successful eradication regimen with KRG supplementation accompanied with *in vitro* proof showing KRG was very effective in suppressing the CSE/CBS gene led to the following conclusion: *H. pylori* infection might be closely responsible for halitosis and KRG supplementation was proven to be very effective in relieving halitosis in addition to being responsible for bacterial suppression (Figure 2B). In addition, generally good short-term results were reported with chlorhexidine. Triclosan seems less effective, essential oils and cetylpyridinium chloride are only effective up to 2 or 3 hours. Metal ions and oxidizing agents, such as hydrogen peroxide, chlorine dioxide, and iminium, are active in neutralizing volatile sulfur-containing compounds [48,49], but these are only for lessening halitosis not removing etiopathogenic background.

In conclusion, though the solution of halitosis problems must include the reduction of the intraoral bacterial load and/or the conversion of VSCs to nonvolatile substrates [50], targeting both etiologic organism removal and VSCs generating enzyme suppression seems to be very ideal modality of halitosis treatment (Figure 3), in which KRG seems to ideal product to deserve in clinic.

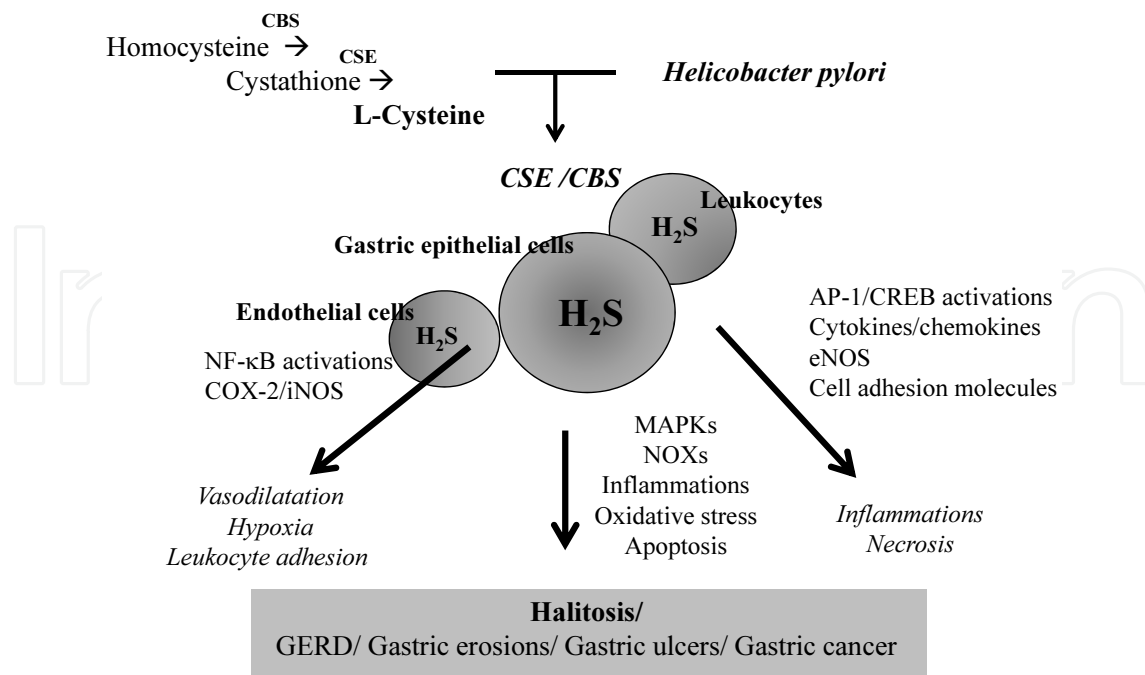


Figure 3. *H. pylori* infection caused halitosis as well as overt clinical diseases relevant to H₂S generation. Dietary sources of L-cysteine and *H. pylori* infection provoked CBS/CSE activations, leading to increased H₂S generation. Currently dual edged biological actions of H₂S were reported; one was vasodilatation and antioxidative actions, and the other the aggravation of inflammations and hypoxic condition. In the stomach under *H. pylori* infection, H₂S-driven gastric surface destruction as well as gastritis finally rendered gastric diseases such as erosive gastritis or ulcerative lesions. Also halitosis was significantly manifested as extragastric symptoms associated with *H. pylori* infection due to significant associations and amelioration of halitosis after eradication.

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Author details

Kyu Hyun Han¹, Jong-Min Park², Young-Min Han², Joo Young Cho¹, Weon Jin Ko¹ and Ki Baik Hahm^{1,2*}

*Address all correspondence to: hahmkb@cha.ac.kr

1 Digestive Disease Center, CHA University Bundang Medical Center, Seongnam, Korea

2 CHA Cancer Prevention Research center, CHA Bio Complex, Seongnam, Korea

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