Dietary, non-microbial intervention to prevent *Helicobacter pylori*-associated gastric diseases

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Abstract: Since the discovery of *Helicobacter pylori* (*H. pylori*) infection as the major cause of gastroduodenal disorders including acute and chronic gastritis, gastroduodenal ulcer, chronic atrophic gastritis, and gastric cancer almost three decades ago, the possibility of preventing these clinical diseases through eradicating *H. pylori* has been the focus of active research, but soon debate in the scientific community, though eradication opens the feasibility of cancer prevention and the removal of bacteria significantly prevents development or recurrence of peptic ulcer diseases and some clinical diseases, was proposed due to uncertainty in either achievement of complete eradication or inefficacy in cancer prevention with eradication alone. Still its linkage to gastric cancer is incontestable. Since the multiple combination of bacterial factors, environmental insults, and the host immune response that drives the initiation and progression of mucosal atrophy, metaplasia, and dysplasia toward gastric cancer is intervened, simple eradication deemed the feasibility of cancer prevention. Therefore, our group open strong hypothesis that non-microbial, dietary approach might be the alternate, for which several interventions of nutritional components can highlight rejuvenation of chronic atrophic gastritis as well as amelioration of *H. pylori*-associated procarcinogenic inflammation. In this review article, the experience and outcome regarding nutritional application to rejuvenate gastric atrophy will be introduced, using Korean red ginseng, garlic extracts, cancer preventive Korea kimchi, n-3 polyunsaturated fatty acids (PUFA), special form of licorice, and probiotics. The detailed influence of dietary intervention and bacterial eradication therapy on disease progression and reversibility of premalignant lesions are discussed.

Keywords: *Helicobacter pylori* (*H. pylori*); gastritis; rejuvenation; carcinogenesis; prevention & control

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Introduction

Helicobacter pylori (*H. pylori*) infection has commonly been accepted to be a cause of acute and chronic gastritis, gastric and duodenal ulcer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma as well as to be associated with extragastric diseases such as iron deficiency anemia, idiopathic thrombocytopenia, atherosclerosis and chronic headache, etc. (1). Particularly, supported with the fact that recurrence or complication of peptic ulcer and several extra-gastric associated diseases can be treated by eradication therapy as well as the result that *H. pylori* could be a direct cause of epigastric pain in functional gastric disorder, *H. pylori* infection has been thought to be an important infectious bacteria as a big etiology of various gastric diseases as well as bacteria satisfying evidence based medicine (2).

In spite of these positive associations, the biggest part among the several unmet medical needs which have been controversial until now is "the association with development of gastric cancer". In various molecular and biologic studies (3) using *in vitro* and *in vivo* models, *H. pylori* infection

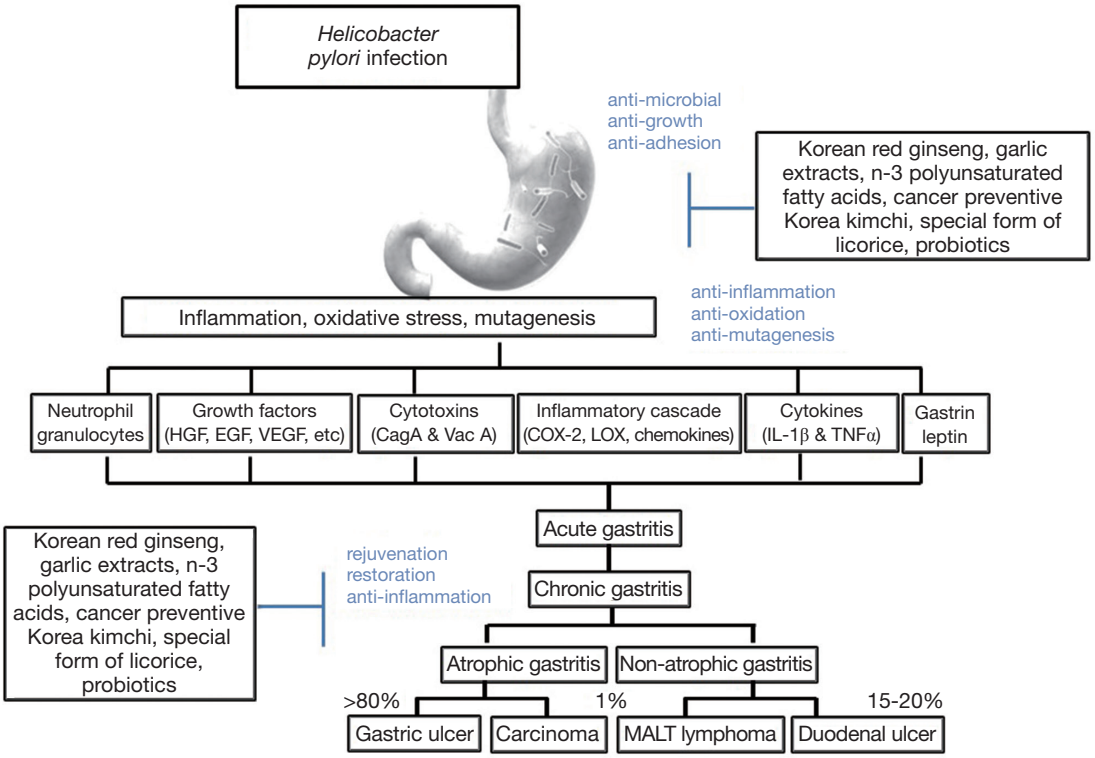

Figure 1 A non-microbial approach for *H. pylori*-associated gastritis as well as gastric cancer supplementation or treatment with long-term phytoceuticals or other agents were proven to be very efficacious in the prevention of *H. pylori*-associated gastric carcinogenesis. These treatment strategies are supported by the clear mechanisms of anti-inflammation, anti-oxidation, and anti-mutagenesis associated with their use. *H. pylori*, *Helicobacter pylori*; n-3, omega-3; COX-2, cyclooxygenase-2; LOX, lip-oxygenase; IL-1β, interleukin-1 beta; TNFα, tumor necrosis factor alpha; MALT, mucosa-associated lymphoid tissue.

has been reported as a direct or promoting factor for gastric cancer development. Also previous clinical cohort or clinical studies proved that gastric cancer development was significantly associated with *H. pylori* infection (4) as well as that gastric cancer recurrence rate was significantly lower in *H. pylori* eradication group after gastric mucosal resection (5). In addition, based on the diverse strong evidences that *H. pylori* eradication can be a method of gastric cancer prevention, starting from 2013 in Japan, national wide strategy that all national people with chronic gastritis infected with *H. pylori* should get the eradication therapy has been under progress (6). However, the approach to make guideline of gastric disease treatment with *H. pylori* eradication has been concluded to be very careful because of several reasons such as the opinion that *H. pylori* eradication is not necessary considering the over 50% of incidence in world's population, the report that only partial people group show efficacy of *H. pylori* eradication, the appearance of antibiotic resistant bacteria strain and the opposite opinion (7) of some researchers who accept *H. pylori* as a commensal bacteria.

Recently, based on the results that inflammation is important pathogenesis between *H. pylori* infection and gastric cancer development and that some of chronic atrophic gastritis is reversible and regeneration to non-atrophic condition is possible, increasing opinion arise that several plant nutrients, probiotics and anti-oxidants which have no side effect in long term administration can suppress the gastric carcinogenesis as well as impose significant regenerative effects (8). Based on hypotheses (8) that diverse food nutrients can reduce inflammation induced by *H. pylori* infection, eradication can reduce atrophic gastritis based on patient's self-regeneration ability and the accumulation of these phenomena can ultimately prevent gastric cancer development, several preclinical and clinical trial studies regarding disease prevention through dietary nutrients are currently in progress. Those studies will be introduced in this review article (*Figure 1*). As examples,

Korean red ginseng and special form of licorice (clinical trials have already been finished for both of them) as well as development of cancer-preventive Korea Kimchi based on material which was proven to have suppressive effect on gastric cancer development will be introduced in this review.

The effect of Korean red ginseng on *H. pylori* infection: augmented eradication rate and rejuvenating action of atrophic gastritis

H. pylori infection was the main risk factor of chronic gastritis and gastroduodenal ulcers (1,2), International Agency for Research on Cancer (IARO) defined the *H. pylori* infection was group I carcinogen in 1994 and revised version was released at 2014 (3). *H. pylori* infection induced chronic inflammation, and provided tumor microenvironment crucial to cancer initiation, survival of tumor cell, progression of cancer, so chronic inflammation had a key role on *H. pylori*-associated gastric cancer. Therefore, it was important to eradicate *H. pylori* infection or attenuate chronic inflammation for prevention of *H. pylori*-associated gastric cancer. The Korean red ginseng attenuated 5-lipoxygenase (LOX) activity, which is important mechanism on carcinogenesis. In other words, long term application of the Korean red ginseng expected suppression of development of *H. pylori*-associated gastric cancer (9). Also, extracts of Korean red ginseng had preventive effect of gastric mucosa cytotoxicity, which interrupted apoptosis by blocking receptor signaling pathway on *H. pylori* induced gastric mucosal injury, reduced binding of NF-κB with DNA. Until the present, it was known that the efficacy of Korean red ginseng was anti-oxidative, anti-inflammatory effect (10-13), these effects were based on the facts that ginsenoside Rb1 suppressed the expression of tumor necrosis factor alpha (TNF-α) induced by lipopolysaccharide (14), and the acidic polysaccharide, panaxytriol interrupted *H. pylori* colonization and attachment on gastric mucosa (12,15). Extracts of Korean red ginseng suppressed production of hydrogen sulfide (H_2S) on *H. pylori* infected gastric mucosa, then prevented significant mucosal injury, inhibited halitosis, suppressed carcinogenesis-related angiogenesis (16,17). Through clinical trial, the authors investigated the efficacy of Korean red ginseng on *H. pylori* eradication rate, and confirmed significant improvement of eradication rate after 10 weeks treatment of Korean red ginseng after conventional *H. pylori* eradication regimen. In conclusion, the application of Korean red ginseng improved the eradication rate and was superior in quality, in order to receive recognition as a guideline, additional large scale randomized prospective trials were needed.

The effect of garlic extracts on *H. pylori* infection: anti-inflammatory and anti-mutagenic activity

Garlic (*Allium sativum L.*) is one of the most widely grown vegetable crops in Asia including Korea. Garlic has long been used as a seasoning or condiment for its pungent flavor for a long time. Garlic is also known as a medicinal food ingredient with physiological potential since ancient times (18). Garlic contains at least 33 sulfur compounds such as allicin, alliin, ajoene, diallyl trisulfide (DATS) and others. The sulfur compounds are responsible many of its medicinal effects; antioxidant, antiinflammation, antimutagenic, haematological, antimicrobial, hepatoprotective and antineoplastic properties. In particular, oil-soluble sulfur compounds [e.g., sulfoxides (alliin), diallyl sulfide (DAS), diallyl disulfide (DADS), DATS] and water-soluble sulfur compounds, e.g., S-allylcysteine (SAC) and S-allyl mercaptocysteine, have all been shown to exhibit antimicrobial, antioxidant and antiinflammation activity (19). In recent, several studies reported that sulfur compounds have effects to inhibit *H. pylori* colonization, decrease gastric inflammation and oxidative stress by *H. pylori* infection, and lead gastric ulcer healing. Many preparations of garlic with different compositions of bioactive compounds are commercially available (20,21). Among these preparations (water, acetone, ethanol, and hexane), ethanol and acetone extracts showed the highest bacteriostatic activities against *H. pylori* (22). Garlic oil extracts also exhibited direct anti-*H. pylori* effects (23). Antimicrobial activity of the DAS increased with the number of sulfur atoms (24). Allicin and methyl-allyl thiosulfinate from acetonic garlic extracts have shown inhibition of the *in vitro* growth of *H. pylori* (25). *In vivo* study, garlic extract prevents *H. pylori*-induced gastritis in Mongolian gerbil model (26). In clinical reports, Gail *et al.* (27,28) showed that the ingestion of garlic supplement significantly reduce the prevalence of gastritis in Linqu County, Shandong Province, China, a region with high gastric cancer mortality rates and a prevalence in adults of *H. pylori* of approximately 67%. Fani *et al.* (29) suggested combined garlic and omeprazole instead of the standard quadruple therapy for the eradication of *H. pylori* infection (29).

In our recent study, SAC, a water-soluble garlic compounds that had been known to possess a powerful anti-oxidant property, has been shown to exert antiinflammatory and mucosa protective effects against gastrointestinal (GI) inflammation. Especially, SAC significantly prevents *H. pylori*-induced gastritis *in vivo*. SAC significantly inhibited pro-inflammatory signaling, including cyclooxygenase-2 (COX-2), TNF-α, interleukin-1 beta (IL-1β) and interleukin-6 (IL-6), and decreased in macrophage infiltration as well as gastric cell proliferation. Moreover, SAC suppressed *in vitro* growth of *H. pylori*. Finally, these results suggest that garlic extracts and compounds can be a gastroprotective agent against *H. pylori*-induced gastric mucosal damage and gastric cancer.

The preventive effects of omega-3 polyunsaturated fatty acids (n-3 PUFAs) on *H. pylori* infection-associated atrophic gastritis and gastric tumorigenesis

Omega-3 is polyunsaturated fatty acids (n-3 PUFAs) with a double bond at the third carbon atom from the end of the carbon chain. It is known to prevent anti-cancer, anti-oxidant and anti-inflammation (30). The three types of n-3 PUFAs involved in human physiology are α-linolenic acid (ALA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Common sources of plant oils containing the n-3 ALA FA include walnut and seed oil, while sources of animal n-3 EPA and DHA FAs include fish oils and egg oils. Since mammals can't synthesize n-3, we must get n-3 from drugs or foods (31). Many research groups studied about between n-3 and cardiovascular diseases who reported that n-3 PUFAs have effects for function recovery of the coronary arteries, plaque reduction of atherosclerosis and inhibition of inflammatory cytokines which take effects through inhibition of NF-κB signaling (30-32). Recently several investigators have examined the anti-inflammatory effects of n-3 on *H. pylori*-induced gastric diseases because n-3 FAs affect lipid raft assembly and its functions by reducing membrane fluidity of bacteria (32,33). Lipid raft is microdomain having abundant cholesterol of cell membrane which is essential for anti-inflammatory action because NF-κB activation dependent inflammation actively occurred after *H. pylori* infection (34). Correia *et al.* (35) reported that DHA significantly decreased the inflammation of gastric mucosa by reducing growth of *H. pylori* in dose-dependently *in vivo* and *in vitro*. All of these data suggested that DHA is possible as supplementary drug on either removal treatment of *H. pylori* or attenuation of inflammation. However, Meier *et al.* (36) showed that removal treatment of *H. pylori* with n-3 have no statistically significant compare with general removal treatment methods. Therefore our study group investigated effects of n-3 FAs in *H. pylori* induced gastritis. n-3 PUFAs decreased oxidative stress and inflammation induced by *H. pylori* infection in normal gastric mucosa cells. To check the effects for anti-inflammation and anti-cancer of n-3 PUFAs in *H. pylori* infection we performed long period animal model. In 45 weeks after *H. pylori* infection, wild type mice indicated not only gastric cancer formation with atrophic gastritis but also autophagy and lipid raft disturbance more than n-3 PUFAs treated mice. Recently, Kuriki *et al.* (37) suggested that there is no correlation between erythrocyte composition and disease incidence of gastric cancer in human study. Conclusively, in order to demonstrate the preventive or therapeutic effects of n-3 PUFAs for gastric diseases induced by *H. pylori* infection, large scale clinical and detailed mechanism study. If we have results about that long-term administration of n-3 PUFAs have preventive effects for gastritis and *H. pylori*-induced tumorigenesis, might be an example of cancer prevention through foods.

Cancer preventive—kimchi

Korea and Japan are similar to gastric carcinogenesis environment. In Japan, the eradication of *H. pylori* from patients with chronic gastritis as a way of cancer prevention start the effort to reduce the occurrence of cancer from this year. Kimchi is representative fermented, antioxidant food and a safe food for thousands of years been ingested in Korea. If we can make a specially reciped kimchi, it hypothesized this would be an ideal food with cancer prevention. The following experiment was in our laboratory. Several researchers have found that *Lactobacillus plantarum* (*L. plantarum*) derived from kimchi can promote suppressor of cytokine signaling (SOCS) secretion (38,39). To explore the effects of specially reciped kimchi containing phytoceutical on *H. pylori*, *H. pylori* infected wild type mice were sacrificed after 24 weeks and after 36 weeks. Among them, one group was fed drinking water containing extract of cancer preventive kimchi. As a result, *H. pylori* infection group was found severe inflammation, mucosal erosion, dysplasia, adenoma of the stomach. However, the group fed with cancer preventive kimchi was reduced significantly. Furthermore, *H. pylori* infection group increased COX-2 expression, NF-κB and p-STAT3. But redesigned kimchi

group reduced COX-2, NF-κB and p-STAT3 expression and increased antioxidant enzyme such as heme oxygenase-1 (HO-1) compared to *H. pylori* infection group. In addition, we confirmed that a specially reciped kimchi reduced *H. pylori*-induced inflammation enzyme; COX-2, inducible nitric oxide synthase (iNOS), TNF-α, and induced apoptosis to gastric cancer cell specifically. Taken with all these evidences, it is expected to possible cancer preventive kimchi development for gastric cancer prevention specially formulated with well-known anti-cancer phytochemicals.

Special form of licorice for *H. pylori* infection

Licorice extracts derived from dried root of *Glycyrrhiza* species, which is widely used as drugs in East and West are known to be have preventive effects for GI disease. Licorice extracts contained biologically active substance including glycyrrhizin, licochalcone A, licorisoflavan A etc. (40). Recently several research groups suggested that licorice extracts and its biologically active substance have effects of detoxification, antioxidant, anti-inflammation, anti-bacteria and anti-cancer. Nevertheless licorice whole extracts were limited to use due to the side effects by glycyrrhizin. Therefore our research group studied that special licorice extracts (s-lico) have preventive effects for *H. pylori* induced gastritis *in vitro* and *in vivo*. S-lico contained low glycyrrhizin and high lico. When stomach was infected by *H. pylori*, generally ROS production was increased which affect inflammation and tumorigenesis in stomach. Thus, we measured ESR (electron spin resonance) and dichlorofluorescin diacetate (DCFDA) to check the ROS-scavenging activity of s-lico *in vitro*. As a result, s-lico had significant scavenging activity for ROS and *H. pylori* treated cells showed that ROS generation was increased but *H. pylori* and s-lico (10 μg/mL) treated cells were decreased ROS generation in DCFDA. Therefore s-lico had ROS-scavenging activity through anti-oxidant effects against *H. pylori* infection. Moreover we examined inflammatory associated factors including COX-2, iNOS and TNF-α. After *H. pylori* infection, inflammatory factors were increased whereas s-lico decreased the expression of COX-2, iNOS and TNF-α *in vitro*. Several studies reported that *H. pylori* infection induced inflammation and tumor by strong angiogenesis activity in stomach. So, to determine that s-lico had effects for angiogenesis, we checked the VEGF expression as known angiogenesis marker in cancer cells. As a result s-lico exposed cells significantly declined the expression of VEGF. It is important that s-lico decreased angiogenesis activity by *H. pylori* infection so s-lico was useful as potential candidate material in augmented angiogenesis activity of cancer cells. To demonstrate whether preventive effects of s-lico validated *in vivo*, we performed animal experiment using mice. Wild type mice were infected by *H. pylori* and then sacrificed after 24 weeks. We divided three groups including non-treated group, *H. pylori* infected group and diet contained s-lico intake group with *H. pylori* infection. As a result, *H. pylori* infected group showed higher score of inflammation, mucosal erosion, dysplasia and adenocarcinoma in stomach but s-lico intake group indicated remarkably lower level about stomach lesion. And *H. pylori* group elevated the expressions of basic fibroblast growth factor (bFGF), intercellular adhesion molecule 1 (ICAM1), TNF-related activation induced cytokine (TRANCE) and TNF receptor superfamily, member 19 (TNFRSF19/TROY) as angiogenesis associated cytokines. On the other hand, s-lico treated group reduced the levels of angiogenesis related cytokines. The COX-2 expression was increased in *H. pylori* group and prostaglandin E2 (PGE2) as product of COX-2 also was high expression. However, s-lico intake group decreased COX-2 and PGE2 levels together with inflammatory cytokines including TNF-α, IL-1β and IL-6 etc. Taken together, we supported that s-lico had effects of anti-oxidant, anti-inflammation and anti-cancer in inflammation related carcinogenesis with gastritis thus, s-lico may affects preventive effects for stomach disease by *H. pylori* infection.

Probiotics as alternative therapies for *H. pylori* infection

Probiotics, non-pathogenic microbial feed, are already being widely applied in the treatment of GI infections and GI diseases including irritable bowel syndrome, inflammatory bowel disease, pancreatitis, and liver diseases as an alternate way to enhance anti-microbial and anti-inflammation (41-45). In clinical reports, the addition of probiotics to proton pump inhibitor (PPI)-based triple therapy augmented the likelihood of successful *H. pylori* eradication. In particular, probiotics competed directly with *H. pylori* as well as reduced *H. pylori* associated inflammation (46-48). *L. salivarius* significantly decreased gastric epithelial cell chemokine, such as interleukin-8 (IL-8), production responses to *H. pylori* infection. *L. acidophilus* reduced *H. pylori*-induced inflammation through the inactivation of the Smad7 and NF-κB pathways. *L. plantarum*, *L. rhamnosis* and *L. acidophilus* all could ameliorate *H. pylori*-induced inflammation by either efficiently activating

SOCS expression or inactivating the janus kinase 2 (JAK2) signaling pathways. Several human studies have investigated the efficacy of probiotics for the treatment of *H. pylori* infection (49-51). Most of the studies reported an improvement of *H. pylori* gastritis and decrease in *H. pylori* colonization after administration of probiotics. However, none of the studies could demonstrate complete eradication of *H. pylori* by probiotic alone (45,52,53). In a recent, a growing body of experimental and clinical evidence has supported the importance of intestinal microbiota, in *H. pylori* infection as well as the onset of GI diseases. Probiotics, as live organisms, can modulate the human microbiota and promote health, prevent antibiotic side effects, stimulate the immune response and directly compete with pathogenic bacteria (54). *L. species* are acid-resistant and commensal and their concentrations in the normal human stomach vary between 0 and 10^3 mL^{-1}. They can survive in the stomach for periods of up to 2 h. Therefore, the administration of probiotics, such as Lactobacillus species, can perturb microbiota in the *H. pylori* infected stomach. Finally, the advantages attributed to probiotics in *H. pylori* infection, such as improvement of the eradication rate, reduction of side effects associated with eradication drugs, and some direct anti-inflammatory action, may represent only a small part of their advantages. Extensive investigation of the microbiota relevant to *H. pylori* infection will be required to elucidate additional mechanisms and relationships.

Conclusions

Modern evidence-based medicine (EBM) has big difference from the traditional oriental medicine only based on experiences. In other words, noble medical technology can be available through strict verification of clinical trial with double blind condition (55). The verification of multi-centers through long term observation is necessary for food nutritional approach for the prevention of *H. pylori* associated diseases through the control of *H. pylori* infection. In addition to guideline for *H. pylori* eradication, long term approach with food nutrients could be a noble treatment method to solve the unmet medical needs related with *H. pylori* infection (*Figure 1*). Particularly, cancer-preventive Korea kimchi which we are recently developing as well as all national people eradication plan in Japan from 2013 deserve to have a trial considering that the incidence of gastric cancer is continuous and mortality rate of that is about 20 per 100,000 population (in Korea) and about 50 per 100,000 population (in Japan), which clearly means novel approach could reduce the mortality rate of gastric cancer in these high risk countries. Korean red ginseng has been proven to have safety because Korean people have had it over 100 years, which is similar to a kind of clinical trial. Therefore, the clear evidence based medical (EBM) approach grounded on well constituted clinical trial plan is needed on plausibility of *H. pylori* control by these food nutrients.

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