Korean Red Ginseng: Qualitative and Quantitative Benefits on *Helicobacter pylori* Infection

Jun Won Chung, Yoon Jae Kim, So Jung Lee, and Ki Baik Hahm*

Department of Gastroenterology, Gachon Graduate School of Medicine Gil Medical Center, Incheon 405-760, Korea

Ginseng has been reported to reduce the risk of cancer in diverse organs, including the lip, oral cavity, pharynx, larynx, esophagus, lung, liver, pancreas, ovary, colon, rectum, and stomach, as demonstrated in clinical and epidemiological studies. studies, base on which findings, *Panax ginseng* has been classified as a “non-organ-specific cancer preventive.” However, the recent keen interest in traditional medicinal herbs has been frequently questioned, about exact mode of action and the use of panaceic compounds has been a prime issue discussed in terms of complementary and alternative medicine. Several *in vitro* and *in vivo* studies have shown the mitigating effects of Korean red ginseng on *Helicobacter pylori* (*H. pylori*)-associated atrophic changes and carcinogenesis; However, evidence-based medicine, consisting of large-scale or well designed clinical studies, is still warranted whether Korean red ginseng is to be recognized as an essential therapeutic strategy regarding a “*H. pylori*-associated gastric cancer preventive.” Specifically, comprehensive clinical trials of Korean red ginseng are needed to demonstrate that mucosal regeneration in patients with atrophic gastritis is feasible using Korean red ginseng supplements after the eradication of *H. pylori* infection. Ginseng is a good example of a natural herb and its ubiquitous properties may include the reduction or delay of inflammation carcinogenesis. Korean red ginseng contains ample amounts of active ginsenosides and we have demonstrated their effects in *in vitro* and *in vivo* studies with positive outcomes. In this review, the quantitative and qualitative benefits of Korean red ginseng in the treatment of *H. pylori* infection are described.

Keywords: Korean red ginseng, Gastritis, Carcinogenesis, Rejuvenation, Cancer prevention, Halitosis, Eradication

INTRODUCTION

An overview of *Helicobacter pylori* infection

The discovery of the bacterium *Helicobacter pylori* (*H. pylori*), resident in the human stomach, as the causal agent of chronic disease including chronic gastritis, peptic ulcer diseases, and gastric cancer, was revolutionary in gastroenterology. Whereas the mouth and the colon were both known to host a large number of microorganisms, collectively referred to as the microbiome, the stomach was thought to be virtually sterile because its high acidity provides a very harsh environment for pathogens [1]. However, many species of bacteria are

known reside in the stomach and that, among them, *H. pylori* seems to dominate [2]. Moreover, *H. pylori* was the first bacterium documented to behave as a carcinogen and it has been classified by the World Health Organization’s International Agency for Research on Carcinogenesis (IARC) as a class I carcinogen [3-5]. While little doubt exists that *H. pylori* infection is a major factor in the pathogenesis of gastritis, gastroduodenal ulcer disease, and chronic atrophic gastritis (CAG), these diseases seems to originate from a complex interaction among the bacterium, the host, and the gastric environ-

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*Corresponding author

E-mail: hahmkb@gachon.ac.kr

Tel: +82-32-899-6055, Fax: +82-32-899-6054

ment. Accordingly, the eradication of *H. pylori* in asymptomatic individuals may not be the sole approach to sever these connections, nor is it clear why some people remain asymptomatic while in others, infection with the bacterium leads to the development of gastric cancer.

H. pylori infection: pathogenic roles from gastritis to gastric cancer

H. pylori colonize the stomach of more than half of the world's population, with infection playing a key role in the pathogenesis of many gastroduodenal diseases (Fig. 1a).

Fig. 1. Gastric diseases associated with *Helicobacter pylori* (*H. pylori*) infection. (a) *H. pylori* infection is associated with various gastric diseases, including acute and chronic gastritis, chronic atrophic gastritis, and gastric malignancies (mucosa-associated lymphoma tissue [MALT] lymphoma and adenocarcinoma). However, over 80% of adults infected with *H. pylori* remain asymptomatic, such that treatment guidelines remain controversial. (b) Pathogenic mechanisms of *H. pylori*-associated gastric mucosal damage include increased cytokine production, oxidative stress, and abnormally high rates of apoptosis, all of which contribute mechanistically to *H. pylori*-associated gastric mucosal injuries. (c) Signal transduction in response to cytokine generation after *H. pylori* infection. TBA-RS, thiobarbituric acid reactive substance; GRO- α , growth related oncogene- α ; GSH, reduced glutathione; GSSG, oxidized glutathione; GSH-Px, glutathione peroxidase; NF- κ B, nuclear factor-kappaB; IKK, inhibitory κ B kinase; AP-1, activator protein-1; MEK1/2, MAP kinase kinase; ERK1/2, extracellular signal related kinase 1/2; ELK, *ets* oncogene family as *ets* related transcription factor.

However, not all *H. pylori* strains have the same ability to cause gastric diseases, with host genetic background, environment, diet, hygiene, and cross talk between bacterial gene products and host cells as additional determining factors. Colonization of the gastric mucosa with *H. pylori* results in the development of chronic gastritis in most infected individuals, the clinical outcome of which is dependent on many variables, including *H. pylori* genotype, innate host physiology, host genetic predisposition, and environmental factors. However, a subset of these patients experience progression to complications such as peptic ulcer disease, gastric neoplasias, and extragastric disorders [6]. Since *H. pylori* eradication decreases the incidence of gastroduodenal ulcer and prevents its recurrence, CAG and gastric cancer have become the focus of great interest in terms of the feasibility of disease reversal or chemoprevention following eradication of the bacterium. A meta-analysis of studies on the association between *H. pylori* infection and CAG that were published until July 2007 was carried out by Weck and Brenner [7], with separate meta-analyses of studies defining CAG based on gastroscopy with biopsy, serum pepsinogen I (PG I) only, the PG I/pepsinogen II (PG II) ratio only, or a combination of the PG I and PG I/PG II ratios. The number of analyzed studies (*n*) and the summary odds ratios (ORs) (95% confidence intervals) were as follows: gastroscopy with biopsy: *n*=34, OR=6.4 (4.0-10.1); PG I only: *n*=13, OR=0.9 (0.7-1.2); PG I/PG II ratio: *n*=8, OR=7.2 (3.1-16.8); combination of PG I and PG I/PG II: *n*=20, OR=5.7 (4.4-7.5). Studies with CAG definitions based on gastroscopy with biopsy or the PG I/PG II ratio (alone or in combination with the PG I) yielded similarly strong associations of *H. pylori* with CAG. These findings led to the conclusion that if the appropriate timing for intervention can be determined or an effective means of bioregulation of *H. pylori*-associated events identified, controlling CAG and gastric cancer will be possible. The importance of these capabilities is further underlined by the fact that, in addition to CAG, infection with *H. pylori* is associated with other extragastric conditions, including respiratory disorders (chronic obstructive pulmonary disease, bronchiectasis, lung cancer, pulmonary tuberculosis, bronchial asthma), vascular disorders (ischemic heart disease, stroke, primary Raynaud phenomena, primary headache), autoimmune disorders (Sjögren syndrome, Henoch-Schönlein purpura, autoimmune thrombocytopenic purpura [ITP], autoimmune thyroiditis, Parkinson's disease, idiopathic chronic urticaria, rosacea, alopecia areata), and other

conditions (iron deficiency anemia [IDA], growth retardations, liver cirrhosis) [8]. However, case studies, small patient series, and nonrandomized trials that have shown a beneficial effect of *H. pylori* eradication under different conditions are not convincing, and according to the Maastricht III criteria, the only conditions in which *H. pylori* eradication indicated are ITP and IDA [9].

A cross-link between *H. pylori*-associated CAG and gastric cancer

The discovery of *H. pylori* as the causative pathogen of gastric cancer has raised hopes that the malignancy can be prevented through bacterial eradication, as epidemiological research and animal studies have confirmed the IARC (1994) classification of *H. pylori* as a definite carcinogen. This classification was based on theoretical considerations as well as the results of animal experiments showing that infection of *H. pylori* causes inflammatory-type infiltration, oxidative damage, and mutations of the gastric mucosa (Fig. 1b, c) [10-12]. In a resected gastric cancer specimen, intestinal metaplastic lesions were easily identified around cancer lesions. However, the reason why gastric cancer is not controlled after eradication of *H. pylori* can be explained by the sequence "CAG-intestinal metaplasia-gastric cancer"; thus, only those patients who do not yet have malignant disease can be spared *H. pylori*-associated carcinogenesis. Beyond this point, despite *H. pylori* eradication, inflammation in the stomach persists. Accordingly, amelioration of the gastric inflammation rather than simple eradication of the pathogen is generally accepted to be the key to cancer prevention [13]. This implies that chronic gastritis has a greater chance of leading to gastric cancer than infection by *H. pylori* alone. In this view, gastric cancer induced by *H. pylori* is actually the product of CAG and intestinal metaplasia, followed by dysplasia and, ultimately, intestinal malignancy [14,15]. Furthermore, in addition to gastric inflammation, genetic factors, toxicity of the pathogen, and environmental factors combine to promote *H. pylori*-induced gastric cancer subsequent to inflammation. Thus, the common denominator within this broad range of contributing factors and fundamental to the prevention of gastric cancer is the alleviation or attenuation of gastric inflammation.

Non-antimicrobial Therapeutic Approaches to *H. pylori* Infection

While the most effective therapeutic approach to the

eradication of *H. pylori* is the combination of a proton pump inhibitor (PPI) with antibiotics, in 20-30% of patients, the method is not successful. In these patients, antibiotic resistance is a major factor affecting treatment outcome [16-18]. Therefore, non-antibiotic therapies, including phytochemicals, probiotics, and antioxidants, have been increasingly investigated as alternatives in the treatment of *H. pylori* [19-21]. *In vitro* experiments and *in vivo* nonhuman trials have examined the therapeutic potential of ginseng, wine, garlic, propolis, cranberry, green tea, probiotics, and antioxidants (Fig. 2a). *In vivo* human trials, most of which were aimed at determining the effects of supplements following *H. pylori* eradication regimens, tested garlic, capsaicin, cinnamon, probiotics, Chinese herbal medicines, lactoferrin, and antioxidants including vitamin C and E. In some

cases, improved eradication rates or the reduction of the side effects of the various eradication regimens were documented. Kim *et al.* [22] conducted a randomized, open-label study to evaluate whether PPI-based 1-week triple therapy with adjunctive probiotic administration increased *H. pylori* eradication rates and reduced the adverse effects related to triple therapy. The addition of probiotics to triple therapy did not reduce side effects but did increase the eradication rate: 78.7% with eradication therapy alone versus 87.5% with eradication therapy plus 3 weeks of probiotics. Similar results were obtained in rather detailed clinical trials that examined *H. pylori* eradication through a non-antibiotic approach, such as vitamin C, lactoferrin, and vitamin E, and led to the conclusion that these compounds could improve the eradication rates obtained with anti-*H. pylori* therapy and

A Non-microbial approach for *H. pylori* infection

1. Korean red ginseng
2. Green tea polyphenols
3. Probiotics (yoghurt)
4. Licorice
5. Red pepper
6. Garlic
7. Ginger
8. Genistein
9. Red wines
10. Berries

B Chemical structure of ginseng saponins

Protopanaxadiol (PD)

Ginsenoside Rb1
Ginsenoside Rb2
Ginsenoside Rc
Ginsenoside Rd

Protopanaxatriol (PT)

Ginsenoside Re
Ginsenoside Rf
Ginsenoside Rg1
Ginsenoside Rg2

Oleanane

Ginsenoside R0

Fig. 2. Nonmicrobial approach to the treatment of *Helicobacter pylori* (*H. pylori*) infection. (a) Treatment guidelines for *H. pylori* eradication have yet to be established as no clear evidence exists that eradication of the bacterium results in cancer prevention, and gastric inflammation persists even after successful eradication. This has led to increased interest in nonmicrobial approaches to the treatment of *H. pylori* infection, including Korean red ginseng, probiotics, vitamins C and E, garlic, ginger, and propolis. (b) protopanaxadiol and protopanaxatriol, the major components of ginseng saponins, may be the active agents in the therapeutic benefits of ginseng supplementation in *H. pylori* infection.

might be beneficial in patients with eradication failure [23,24]. However, results from a meta-analysis did not provide convincing evidence in favor of supplementary therapy. For example, Chuang *et al.* [25] and other investigators [26] found that in patients with metronidazole-susceptible *H. pylori* infection, the addition of vitamins may even lower the eradication rate of triple therapy. Therefore, whether the regular intake of dietary or dairy products might constitute a low-cost and safe alternative in the prevention of *H. pylori* infection remains to be examined in large-scale or prospective clinical trials.

Korean red ginseng in the mitigation of *H. pylori*-associated gastric inflammation

Several studies have demonstrated the antioxidant, antibacterial, and anti-inflammatory effects of ginseng [27-32]. Ginsenoside Rb1 was shown to inhibit lipopolysaccharide-induced expression of the pro-inflammatory cytokine tumor necrosis factor (TNF)- α , while acidic polysaccharide from ginseng reportedly inhibits the adherence of *H. pylori* to human gastric epithelial cells (Fig. 2b). In addition to these antimicrobial actions, ginseng has distinctive inhibitory effects on the growth of several types of carcinoma cells. Therefore, can ginseng be used to treat *H. pylori*-infected gastric mucosal cells? Our group has documented that Korean red ginseng alleviates *H. pylori*-induced cytotoxicity [27] and mitigates oxidative stress-induced DNA mutation. In addition, Korean red ginseng decreased *H. pylori*-stimulated interleukin (IL)-8 expressions, supporting its use as a medicinal phytonutrient in *H. pylori* infection [21]. Subsequent investigations showed that Korean red ginseng decreases the levels of inflammatory mediators responsible for CAG, intestinal metaplasia, and dysplasia. These anti-inflammatory actions were added to ginseng's cytoprotective or antimutagenic actions.

Preventing precancerous atrophic gastritis: is it possible and then how?

Can the atrophic mucosa characteristic of gastritis be reverted to a non-dysplastic condition either by removal of the bacteria through an eradication regimen or the clearance of gastric inflammation [33]? The answer is "yes, but not all." Although two recent large-scale, prospective studies, both performed in a population at high risk for gastric cancer, confirmed *H. pylori* infection as a definite risk factor for the development of gastric cancer [3, 34], the opposite premise, that the eradication of *H. pylori* infection is an appropriate target for the prevention of gastric cancer, has yet to be confirmed

and remains controversial [35,36]. Three randomized, placebo-controlled trials performed in China and Columbia found no significant protective effect following *H. pylori* eradication [35-37], whereas three recently published Japanese studies [10,13,38] reported that *H. pylori* eradication prevents the development of gastric cancer significantly, even in patients with precancerous gastric lesions. However, these observations did not address the possibility that earlier eradication therapy or other, similar types of intervention aimed at reducing gastric inflammation could be beneficial in high-risk populations [39]. Recently, Fukase *et al.* [40] published important results from their study in which, following endoscopic resection of early gastric cancer, a group of patients were randomly subjected to *H. pylori* eradication treatment, with monitoring at different time intervals. At 3 years, metachronous gastric cancer had developed in only 9 of 255 patients in the eradication group vs. 24 of 250 patients in the control group, leading the authors to conclude that prophylactic eradication of *H. pylori* in atrophic gastritis can substantially reduce gastric cancer rates. Nonetheless, the eradication of *H. pylori* infection might only be beneficial if carried out before gastric disease has passed the "point of no return"; however, with current endoscopy techniques or histopathology, discriminating whether a gastric premalignant lesion has indeed reached this stage is very difficult [12]. Instead, supplementary agents or continuing suppressive therapy to mitigate chronic gastric gastritis may well be a more effective approach to gastric cancer prevention (Fig. 3a). We and other investigators have shown that Korean red ginseng can contribute to preventing the progression of atrophic gastritis and to mucosal reversion in non-atrophic gastritis. In the following, we present several examples of the qualitative advantages conferred by the administration of Korean red ginseng to patients with *H. pylori* infection, including anti-halitosis, anti-inflammation, and chemopreventive effects.

QUALITATIVE ADVANTAGES OF KOREAN RED GINSENG IN *H. pylori* INFECTION

Korean red ginseng in the treatment of halitosis: evidences from *in vitro* observations to clinical applications

Halitosis is a general term describing a range of unpleasant or putrefactive odors emanating from the oral cavity [41,42]. It is a rather common symptom that can be troublesome to patients socially, decreasing self-confidence or limiting social interactions. Due to its

Fig. 3. Korean red ginseng, phytochemicals in the treatment of *Helicobacter pylori* (*H. pylori*) infection. (a) The anti-oxidative, anti-inflammatory, and anti-mutagenic actions of Korean red ginseng may explain its ability to improve gastric inflammation, with potential rejuvenation of the mucosa in atrophic gastritis and the improvement of symptoms such as halitosis. In addition, Korean red ginseng significantly augmented the eradication rates achieved with the current triple therapy. (b) The maintenance of gastric homeostasis is essential in *H. pylori* infection, as studies have suggested that the treatment benefits of *H. pylori* eradication alone are limited to the prevention of gastroduodenal ulcer. MAPK, mitogen activated protein kinase; shh, sonic hedgehog; COX-2, cyclooxygenase-2; HSP70, heat shock protein 70; HO-1, heme oxidase-1; 5-HETE, 5-monohydroxyeicosahexanoic acid; nrf-2, NF-E2-related factor 2.

vague pathogenic basis and the low level of medical concerning, only a few satisfying solution exists for halitosis [43]. When severe, a patient's physician or dentist is likely to advise patients to undergo gastrointestinal examination, as gastrointestinal diseases have been suggested to cause halitosis [44], although critical evidence for a causative relationship is lacking except in the case of *H. pylori* infection [45]. Lee *et al.* [28] showed that *H. pylori* produces volatile sulfur compounds (VSCs) in the presence of cysteine in culture media, and Katsinelos *et al.* [46] reported that eradication of *H. pylori* in patients with functional dyspepsia leads to sustained resolution of halitosis during long-term follow-up. We found that Korean red ginseng can resolve halitosis through either regulation of the genes responsible for VSC synthesis or direct inhibition of *H. pylori* infection. The evidence is as follows: *H. pylori*

increased the levels of cystathionine γ -lyase (CSE) and cystathionine β -synthase (CBS) mRNA, which encode inflammatory cytokines that promote VSC synthesis, and of the inflammatory mediators IL-1 β , IL-8, and IL-6; Korean red ginseng significantly attenuated CSE and CBS mRNA production concomitant with decreased expression of the respective proteins; significant reductions in halimeter ppb levels (<50) were obtained after *H. pylori* eradication and red ginseng supplementation [47]. Thus, halitosis appears to be mechanistically associated with *H. pylori* infection, and Korean red ginseng supplementation following a successful eradication regimen could alleviate troublesome halitosis. In previous publications [48,49], we showed that VSCs in gastric juices were significantly correlated with halitosis and that halitosis could be symptomatic of mucosal damage, including gastric erosions or ulcers. Those studies dem-

onstrated that Korean red ginseng supplementation after *H. pylori* eradication augmented bacterial eradication and conferred significant protection against *H. pylori*-induced mucosal damage [27], thus providing both quantitative and qualitative advantages in *H. pylori*-associated gastric mucosal injuries, including the relief of halitosis.

Limitation of CAG progression with Korean red ginseng

As Korean red ginseng has been reported to confer significant protection against *H. pylori*-induced cytotoxicity and DNA damage *in vitro*, we designed a study to assess the efficacy of red ginseng treatment in patients with *H. pylori*-associated chronic gastritis [49]. The 84 patients with *H. pylori*-associated chronic gastritis were randomly divided into two groups. Of the 42 patients in the placebo control group and 42 in the red ginseng group, 34 and 36, respectively, completed the protocol. All patients received 1 week of triple therapy for the eradication of *H. pylori* and then 10 weeks of either a capsule composed of flour for the placebo group, or red ginseng for the treatment group. All patients underwent an endoscopic examination of gastritis, scored by a visual analog scale and a test for the detection of *H. pylori*. DNA damage was assessed using a Comet assay, and the degree of oxidative DNA damage by immunohistochemical staining of 8-hydroxydeoxyguanosine (8-OHdG). Apoptosis was quantified by TUNEL staining. An analysis of gastritis based on the Updated Sydney System showed significant improvement in the red ginseng group with respect to neutrophil infiltration ($p=0.008$), CAG severity ($p<0.05$), and even intestinal metaplasia ($p=0.005$). An attenuation of 8-OHdG immunohistostaining, DNA damage, and apoptosis ($p<0.001$) after treatment was seen more frequently in the red ginseng group than in the placebo group. These findings recommend the clinical usefulness of Korean red ginseng supplementation in patients with *H. pylori*-associated chronic gastritis (Fig. 3a,b).

Korean red ginseng in the prevention of gastric cancer

Carcinogenesis is a long and multi-step process that includes initiation, promotion, and progression as a consequence of an imbalance between cell proliferation and cell death. The complex inflammatory response involving the epithelial layer and mesenchymal tissues is accompanied by genetic and epigenetic events, which, by conferring distinct advantages in cell growth, lead to the progressive conversion of normal cells into cancer

cells [11,50,51]. A wide array of chronic inflammatory conditions predisposes susceptible cells to neoplastic transformation [52,53]. Inflammatory stimuli include chemicals and foreign bodies (e.g., asbestos, fiber, silica particles, catheters, alcohol, bile acids, gastric acids, gallbladder stones, and ultraviolet light) and infectious organisms (e.g., *H. pylori*, hepatitis B and C viruses, Epstein-Barr virus, herpes virus, human papilloma virus, and human immunodeficiency virus) [54,55]. Inflammatory cells (neutrophils, monocytes, macrophages, eosinophils, dendritic cells, mast cells, and lymphocytes) are recruited after cell or tissue damage or in response to infection and contribute to the onset and progression of cancer [56]. In general, the longer the duration of inflammation, the higher the risk of cancer will be. Moreover, once a tumor develops, the tumor cells continuously stimulate macrophages and other inflammatory cells to promote tumor progression through the production of pro-inflammatory cytokines, including TNF- α , interleukin (IL)-1 β , IL-6, IL-8, interferon- γ , Murine Double Minute 2 (MDM2), p53, and angiogenic factors. Also, an imbalance between reactive oxygen species (ROS)-generating enzymes and antioxidant defense mechanisms is involved, leading to oxidative stress, and an activation of NF- κ B, inducible nitric oxide synthase (iNOS), cyclooxygenase (COX)-2, proteinases, and oncogenes. The trophic nature of the tumor microenvironment facilitates angiogenesis, breakdown of the extracellular matrix, and tumor cell motility [57,58].

Inflammation therefore represents an important therapeutic target for cancer prevention and cure, and numerous chemopreventive agents with inflammation-attenuating activity have been studied, including ginseng, curcumin, retinoids, vitamin E, silimarin, aspirin, celecoxib, plant polyphenols, and PPIs [59,60]. A PubMed search for “cancer” and “*Panax ginseng* (*P. ginseng*)” yielded over 400 articles, reflecting the widespread interest in *P. ginseng* in mitigating carcinogenesis through anti-inflammatory, antioxidant, and anti-apoptotic mechanisms. These publications addressed ginseng-mediated induction of differentiation, specifically, the repair or reverse transformation of hepatoma, melanoma, and teratocarcinoma cells into more differentiated cells, and its effects in reducing chemical carcinogens; inhibiting the development of chemically induced (methyl-N-nitrosourea and N-ethyl-N-nitrosourea) rat mammary adenocarcinoma; and mitigating inflammatory carcinogenesis. The antioxidant effects of ginseng include reductions in COX-2, iNOS,

NF- κ B, and lipid peroxidation, and the scavenging of ROS. The active components of ginsenoside were shown to induce apoptosis and inhibit proliferation as well as cell cycle progression, all of which have been implicated as chemopreventive mechanisms. With the exception of one study to the contrary, ginsenosides were shown to block metastasis and tumorigenesis and to promote immunomodulation [61].

Ginseng has been frequently studied postoperatively and was shown to improve recovery from surgery or illness. Other effects of ginseng include the relief of multidrug resistance (MDR), in the form of enhanced chemosensitizing effects and reduced MDR-related efflux pump activity, and dual angiogenic effects, i.e., anti-angiogenic activity in carcinogenesis and angiogenic activity in the context of healing [30,61,62]. In a representational investigation that provided evidence of the anti-carcinogenic properties of ginseng, Yun [63] carried out a human epidemiology study and a well designed animal study, the results of which were published in *Lancet Oncology* (2001). Yun analyzed the effects of ginseng consumption on the risk of cancer by interviewing 905 paired patients and controls matched by age, sex, and date of admission to the Korean Cancer Center Hospital, Seoul, Korea. A significant decrease in the frequency of cancer cases among those with the highest ginseng intake was found for men ($p < 0.0001$) and women ($p < 0.05$). These results strong support for the cancer-preventing effects of ginseng.

QUANTITATIVE ADVANTAGE OF KOREAN RED GINSENG IN *H. pylori* INFECTION

Given the major role played by *H. pylori* in the pathogenesis of chronic gastritis, atrophic gastritis, gastric and duodenal ulcers, and gastric malignancies, including adenocarcinoma and mucosa-associated lymphoma tissue lymphoma (Fig. 1a) [37], great emphasis has been placed on eradication of the bacterium in infected patients especially in light of the substantial advantages shown for this therapeutic strategy. Thus far, the only exception is in gastric cancer prevention, in which the benefits remain uncertain [36]. According to the Maastricht consensus, the first-line therapy for *H. pylori* eradication is the combination of a PPI or the anti-ulcer agent ranitidine bismuth citrate and clarithromycin plus either amoxicillin or metronidazole [16,18]. The eradication rates obtained with this approach range from 75% to 98% with a median of 80%. However, this implies that treatment will fail in up to 20% of patients, and

the rate is likely to be even higher in areas with a high prevalence of resistant *H. pylori* strains, as in Korea [64]. The recommended second-line therapy is a quadruple regimen composed of tetracycline, metronidazole, bismuth salts, and a PPI. However, the efficacy of these first- and second-line regimens is limited by poor compliance due to the lengthy treatment duration, the number and dose of prescribed drugs, and the mild but unpleasant side effects such as diarrhea, nausea, vomiting, abdominal bloating, and pain. Premature interruption of treatment for any of these reasons increases the likelihood of subsequent bacterial antibiotic resistance [17,65]. Gastroenterologists and microbiologists continue to search for new therapies as the extent of *H. pylori*-related disease has become increasingly evident and have made attempts to relieve the physiologic and pharmacoeconomic burden to patients needing second-line therapy. To increase the efficacy of first-line therapy, several clinical trials have examined extending treatment duration to more than 1 week, the use of higher doses of PPIs, and the introduction of new antibiotics such as quinolone. Other approaches include the use of first-line quadruple therapy and the addition of probiotics, vitamin C, bovine lactoferrin, and other nonantibiotic supplements, including ginseng, wine, garlic, honey, and cranberry [19,66,67].

Based on our previous studies, as discussed extensively in the preceding sections, we carried out a prospective clinical study to confirm whether supplementation of Korean red ginseng indeed increases the likelihood of successful *H. pylori* eradication. Among 76 subjects, 45 patients were enrolled in the eradication-alone group and 31 patients in the eradication plus Korean red ginseng group. Participants were assigned randomly based on patient registration number. All patients had *H. pylori*-associated CAG and the baseline characteristics of the two groups were similar. According to an intention to treat analysis, the eradication rates were 77.4% (24 of 31) in the Korean red ginseng group compared to 51.0% (26 of 45) in the eradication alone group. While this difference was not significant, a per-protocol analysis showed that successful eradication of *H. pylori* was achieved in 24 of 26 patients (92.3%) in the Korean red ginseng group, which was significantly higher than in the eradication alone group (26 of 38, 69.4%; $p < 0.05$). No case of noncompliance occurred in the Korean red ginseng group, whereas one patient in the eradication alone group took the prescribed medications for 3 days only. One patient stopped Korean red ginseng supplementation due to epigastric

pain and bloating, whereas four patients in the eradication alone group discontinued medication due to diarrhea in two patients, dizziness and nausea in one patient, and bitter aftertaste and epigastric soreness in one patient. Four patients were lost to follow-up in the Korean red ginseng group and one patient in the eradication alone group [68].

In a previous published trial, we assessed the eradication rate under the same protocol (i.e., eradication alone vs. eradication plus 10 weeks of Korean red ginseng supplementation), although over a different time course [47,49]. By combining the data from the current and the previous trial to determine the overall efficacy of Korean red ginseng supplementation on the *H. pylori* eradication rate, we found that a 10-week course of Korean red ginseng (Jeongkwanjang red ginseng capsule, 2.7 g/day; Korea Ginseng Cooperation, Daejeon, Korea) supplementation significantly augmented eradication rates (eradication alone group 75 of 102, 73.5% vs. eradication plus Korean red ginseng group 82 of 90, 91.1%; $p < 0.005$). We thus conclude that supplementation of Korean red ginseng can provide quantitative and qualitative benefits in the treatment of *H. pylori* infection, especially in populations with notoriously high incidences of *H. pylori*-associated gastric malignancy. The prevalence of *H. pylori* infection is believed to decrease as socioeconomic status improves [69], with one exception: the prevalence of *H. pylori* infection and associated gastric cancer remains high in Korea and Japan. Two nationwide prevalence surveys performed in 1998 and 2005 among asymptomatic Korean adults found a prevalence of *H. pylori* infection of 66.9% and 59.5%, respectively [70], which was not due to an increase in *H. pylori* infection but to the frequent failure of eradication. Korean red ginseng supplementation will therefore provide dual benefits, by offering qualitative and quantitative improvements to patients with *H. pylori* infection.

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