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REVIEW

Non-microbial approach for *Helicobacter pylori* as faster track to prevent gastric cancer than simple eradication

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Abstract

Although the International Agency for Research on Cancer declared *Helicobacter pylori* (*H. pylori*) as a definite human carcinogen in 1994, the Japanese Society for Helicobacter Research only recently (February 2013) adopted the position that *H. pylori* infection should be considered as an indication for either amelioration of chronic gastritis or for decreasing gastric cancer mortality. Japanese researchers have found that *H. pylori* eradication halts progressive mucosal damage and that successful eradication in patients with non-atrophic gastritis most likely prevents subsequent development of gastric cancer. However, those who have already developed atrophic gastritis/gastric atrophy retain potential risk factors for gastric cancer. Because chronic perpetuated progression of *H. pylori*-associated gastric inflammation is associated with increased morbidity culminating in gastric carcinogenesis, a non-microbial approach to treatment that provides long-term control of gastric inflammation through nutrients and other interventions may be an effective way to decrease this morbidity. This non-microbial approach might represent a new form of prerequisite "rescue" therapy that provides a quicker path to the prevention of gastric cancer as compared to simple eradication.

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Key words: *Helicobacter pylori*; Gastric cancer; Prevention; Atrophic gastritis; Non-microbial approach

Core tip: Gastric cancer is a multi-factorial and multi-step disease associated with various risk factors including environmental and pathogenic microbial chronic inflammation. Pharmaceutical intervention and the eradication strategy can provide rapid relief of acute inflammation but fails to correct the underlying cause of chronic inflammation. A non-microbial approach for modulating *Helicobacter pylori* associated gastric inflammation may be an attractive and rapid alternative to optimize cancer prevention strategies and minimize adverse side effects associated with therapeutic regimens.

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INTRODUCTION

Helicobacter pylori (*H. pylori*), a Gram-negative bacterial pathogen that infects approximately 50% of the world's population, provokes chronic gastric inflammation which is considered a major risk factor for the development of gastric and duodenal ulcers, mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma[1]. In 1994, *H. pylori* was classified as a type I (definite) carcinogen

by the International Agency for Research on Cancer[2]. Although the relationship between *H. pylori* and gastric cancer has been acknowledged by diverse forms of clinical evidence, it is still debatable as to whether eradication can lead to the prevention of gastric cancer[3-5]. Traditionally, treatment for *H. pylori* has focused primarily on eradicating the bacteria from the stomach using a combination of antibiotics, such as amoxicillin and clarithromycin, with a proton-pump inhibitor[6-10]. The eradication rate, however, has been declining due to the increasing prevalence of antibiotic resistance, especially clarithromycin resistance[11-15]. This increase in the prevalence of antibiotic resistance has diminished enthusiasm for the use of many popular *H. pylori* eradication therapies. To overcome this decline in the use of first-line treatment options, bismuth-containing quadruple and sequential therapies are emerging as second-line treatments for *H. pylori* infection[16-21]. Although newer treatments for eradicating *H. pylori* continue to be introduced, research on even more effective eradication regimens continues to be conducted. Unfortunately, literature from all over the world continues to document increases in *H. pylori* resistance to antibiotics and this major obstacle has prompted the introduction of new drugs and treatment schemes. It is also important to note that although removal or amelioration of gastric inflammation has been implicated in the prevention of gastric carcinogenesis, the persistent gastric inflammation observed in *H. pylori*-associated gastric carcinogenesis is not always amelioration by *H. pylori* eradication alone.

Because gastric cancer is a multi-step and multi-factorial disease, not all individuals infected with *H. pylori* will develop gastric cancer. In fact, the multi-factorial processes associated with the development of gastric cancer can give hope to some susceptible individuals that it may be prevented through the eradication of *H. pylori*. Conversely, in cases where chronic inflammation is caused by other environmental factors such as diet, eradication of *H. pylori* may only delay the development of gastric cancer rather prevent it. Importantly, there is no overt biomarker supporting the rationale of *H. pylori* eradication in clinic, although endoscopic findings might be recommended (Figure 1). Moreover, the nationwide cost associated with eradicating *H. pylori* in order to prevent gastric cancer would be prohibitive and represent a burden to socio-economically challenged people in developing countries. Therefore, the strategy of cancer prevention through chemopreventive agents may be the most efficacious way to reduce the global burden of cancer.

Cancer chemoprevention was established by Dr. M. Sporn in 1976 and was defined as "the use of natural, synthetic, or nontoxic chemical substances to reverse, suppress, delay or prevent carcinogenic progression" by Dr. M. Sporn and Dr. W. K. Hong[22,23]. The results of several preclinical and clinical studies have indicated that diverse chemoprevention strategies can decrease gastrointestinal (GI) cancer incidence and mortality rates[24]. Essentially, the chemoprevention strategy involves interventions during all three stages of carcinogenesis, (initiation, promotion, and progression) using chemopreventive agents in order to interfere with tumor promotion or progression and reduce the risk of various cancers. All GI cancers have a unique etiology but share common mechanisms including oxidative stress-induced damage of genomic DNA, modification of cellular proteins and lipids, altered cell signaling, and persistent local tissue inflammation. Therefore, the combination of *H. pylori* eradication, anti-oxidant interventions, interventions to normalize aberrant cell signaling, and anti-inflammatory interventions may be an essential and anticipatory strategy for prevention of gastric cancer. Recently, numerous studies have investigated the potential therapeutic benefits of probiotics, phytochemicals, and antioxidant or vitamin supplementation as chemopreventive agents as well as adjuncts to increase the eradication rates of *H. pylori* infection. In this article, we discuss what is known currently about non-microbial preventive strategies for chronic infection with *H. pylori* which may represent a faster option for cancer prevention *via* enhancement of host adoptive responses as well as removal of inflammation responsible for mutagenesis (Figure 2).

ANTICIPATING NON-MICROBIAL APPROACHES FOR PREVENTING *H. PYLORI*-ASSOCIATED GASTRIC CARCINOGENESIS

Cyclooxygenase and 5-lipoxygenase inhibition

H. pylori-induced inflammatory responses have been associated with high concentrations of phospholipase A_2 (PLA_2) which is an essential enzyme for the release of arachidonic acid (AA). AA metabolites, prostaglandins (PGs) or hydroxyl fatty acids (HETEs), are key mediators in inflammatory responses and are metabolized by cyclooxygenase (COX) and lipoxygenase (LOX)[25]. COX-1 and COX-2 are responsible for the production of inflammatory PGs and 5-LOX increases the release of gastrotoxic leukotrienes (LTs)[26]. Conversely, findings demonstrating that inflammatory responses were decreased by inhibiting COX and 5-LOX led research on COX and 5-LOX inhibitors as attractive medications for anti-inflammatory effects[27-29]. *H. pylori* infection induces higher levels of COX-2 expression, overexpression of which has been detected in various cancers including gastric cancer[30-36]. In this regard, nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for preventing cancers as well as reducing pain and inflammation by inhibiting both COX-1 and COX-2 or COX-2 only[37-39]. Long-term use of NSAIDs attenuated gastric mucosal chronic inflammation induced by *H. pylori* infection suggesting that NSAIDs may be preventive agents of the gastric carcinogenesis associated with *H. pylori* infection[40]. However, the adverse effects associated with the use of NSAIDs may present an obstacle to their use as chemopreventive agents. Traditional NSAIDs non-selectively inhibit both

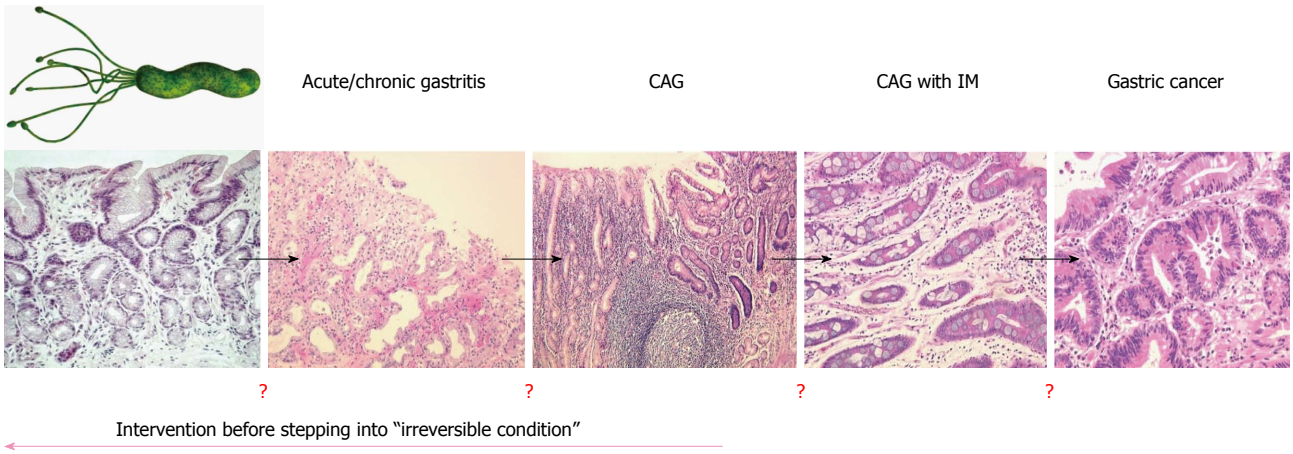

Figure 1 Point of no return in *Helicobacter pylori* infection. *Helicobacter pylori* (*H. pylori*) infection is responsible for acute and chronic gastritis, chronic atrophic gastritis, and intestinal metaplasia. The results of a few studies have shown that the eradication of *H. pylori* significantly reverted these gastric pathologies and promoted restoration of gastric function. *H. pylori* is also implicated in several extragastric manifestations including idiopathic thrombocytopenic purpura, iron deficiency anemia, atherosclerosis, and chronic urticaria. Because there are no biomarkers suggestive of a point of no return, the results of several large scale cohort studies continue to provide support for the strategy of *H. pylori* eradication in gastric cancer prevention.

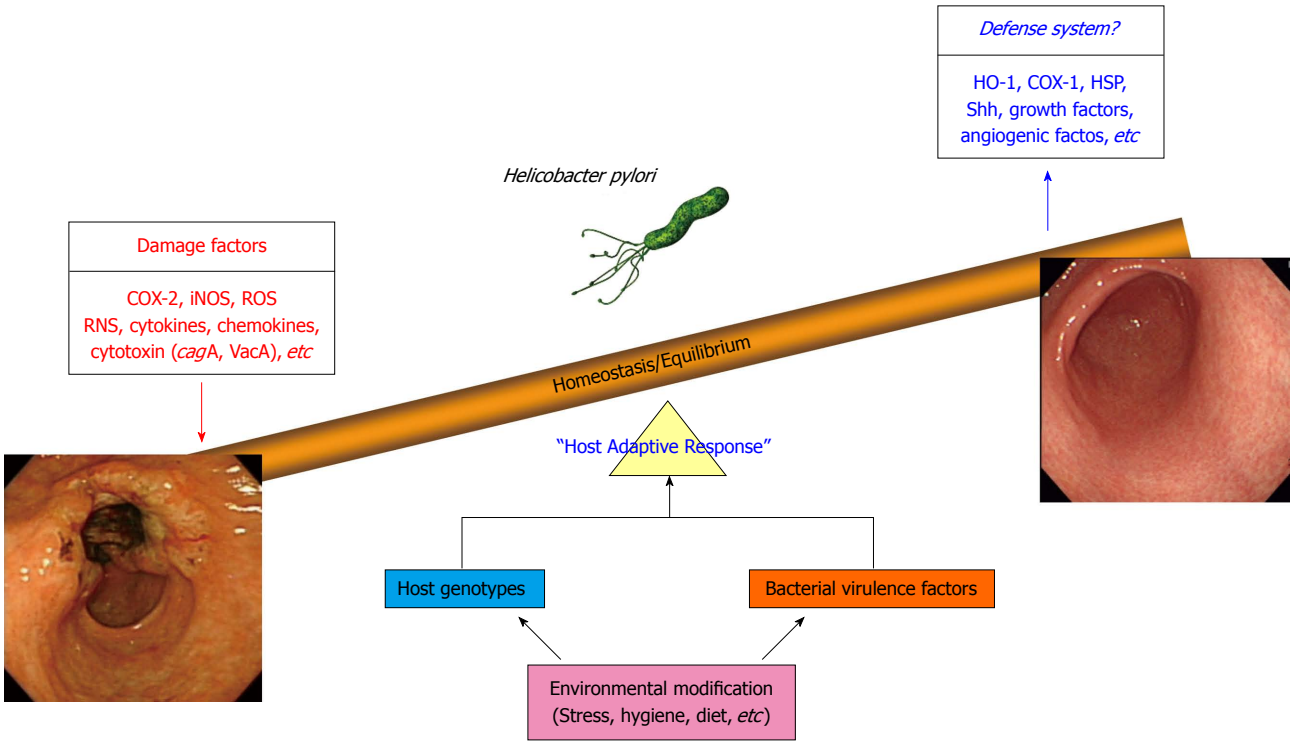

Figure 2 Host adoptive response through a non-microbial approach as the core defensive mechanism against *Helicobacter pylori* infection, especially gastric cancer prevention. Even though host genotype, environmental risk, and bacterial virulence factor are all implicated in *Helicobacter pylori* (*H. pylori*) infection, a non-microbial approach may provide the fastest means of cancer prevention as well as amelioration of *H. pylori*-associated gastric pathologies.

COX-1 and COX-2 and may cause GI toxicity, as COX-1 is a house keeping enzyme involved in the cytoprotection of gastric mucosa. Though selective COX-2 inhibitors (*coxibs*), such as celecoxib, rofecoxib, and valdecoxib, have been developed to improve the GI safety[41], *coxib*s also carry the risk of thromboembolic or cardiovascular complications[42-44]. 5-LOX inhibitors also suppressed *H. pylori*-induced proinflammatory mediators such as interleukin-8 and tumor necrosis factor-α in *H. pylori*-infected gastric epithelial cells, indicating that 5-LOX inhibitors can be preventive agents against *H. pylori*-associated gastric inflammation and carcinogenesis by inhibiting the 5-LOX signaling pathway and suppressing its expression[25].

Phytochemicals and phytonutrients

The results of several recent studies have shown that dietary phytochemicals can modulate key molecular signaling cascades by interacting with small molecules in

cancer cells[45] and that phytochemicals present in foods can inhibit *H. pylori*-induced inflammation. Therefore, the combination of *H. pylori* eradication and the suppression of *H. pylori*-induced inflammation may represent a promising strategy for gastric cancer prevention. For instance, curcumin (diferuloylmethane), the yellow pigment of turmeric (*Curcuma longa* L.) possesses strong anti-inflammatory activities and has shown diverse suppressive actions against various cancers including gastric cancer. It has been reported that curcumin inhibits *H. pylori*-induced nuclear factor (NF)-κB activation, pro-inflammatory cytokines such as interleukin 8, matrix metalloproteinase-3 and -9, and the *H. pylori*-induced motogenic response[46,47]. In addition to these anti-inflammatory and anti-mutagenic actions, curcumin has showed anti-microbial effects in *H. pylori*-infected C57BL/6 mice as well as restorative actions following *H. pylori*-induced gastric damage[48]. Furthermore, curcumin inhibited the proliferation and invasion of gastric cancer cells by suppressing PAK1 activity and cyclin D1 expression[49]. Collectively, the results of these studies suggest that curcumin has potential as an antimicrobial compound and chemopreventive agent against *H. pylori* infection. The results of one recent study suggested that curcumin may prevent cancer therapy-induced oral mucositis due to its antibacterial and anti-inflammatory kinetics[50]. Further research has shown that foods such as broccoli sprouts and oils posses anti-*H. pylori*-associated inflammatory effects mediated by reducing the release of pro-inflammatory cytokines and suppressing the NF-κB pathway[51,52]. Additionally, daily intake of sulforaphane-rich broccoli sprouts was associated with anti-*H. pylori* activity and protection of the gastric mucosa against *H. pylori*-induced oxidative stress[53]. Broccoli sprouts contain high levels of glucoraphanin, a glucosinolate precursor of the isothiocynate sulforaphan known to suppress interleukin (IL)-8 *via* the NF-κB pathway[51,54]. Because *H. pylori*-induced inflammation has been associated with the expression IL-8, a potent neutrophil-attracting chemokine, *via* activation of the NF-κB pathway[55,56], reduction or disruption of this cascade or levels of this cytokine may be an appropriate strategy to intervene in *H. pylori*-induced inflammation.

Omega-3 polyunsaturated fatty acids

There is growing evidence that the diverse biological roles of n-3 polyunsaturated fatty acids (PUFAs) may contribute to their protective actions against chronic inflammatory disease[57]. In bacteria, n-3 PUFAs cause cell lysis, while in other cell types, n-3 PUFAs can be incorporated into membrane phospholipids that can cause a loss of membrane fluidity and may be associated with lipid raft assembly and function[58]. These lipid rafts are cholesterol-rich microdomains at the host cell surface and are required for NF-κB-dependent responses to *H. pylori*[59]. Recently, the results of several studies have suggested that n-3 PUFAs can be converted into bioactive mediators, including resolvins, that have inflammation-resolving properties *via* counter-regulation of lipid mediators such as pro-inflammatory LTs and PGs[52,57]. Correia *et al*[60] conducted experiments that showed that docosahexaenoic acid (DHA) significantly inhibited *H. pylori* growth both *in vitro* and *in vivo* in a dose-dependent manner and decreased mouse gastric mucosa inflammation. These results suggested that DHA could be used as an adjunct agent in *H. pylori* eradication treatment. In contrast, Meier *et al*[61] showed that an n-3 PUFA-containing eradication regimen failed to show any benefit when compared to a conventional eradication regimen. Thus, our group investigated the long-term treatment of n-3 PUFAs in an *H. pylori*-infected animal model and found that long-term administration of n-3 PUFAs ameliorated *H. pylori*-induced gastric inflammation, atrophied gastritis, and attenuated the incidence of *H. pylori*-associated gastric carcinogenesis. Kuriki *et al*[62] conducted a clinical investigation of the association between gastric cancer risk and the erythrocyte composition of DHA using 179 incident gastric cancer cases and 357 non-cancer controls (matched by age, sex, and season of sample collection). The study authors found that the erythrocyte composition of DHA was negatively associated with the risk of gastric cancer, especially of well-differentiated adenocarcinoma. Detailed, randomized, controlled trials should be conducted to obtain strong evidence for the incorporation of nutraceuticals, including n-3 PUFAs, into the therapeutic armamentarium in near future, as their use as therapeutic agents for GI disorders is moving rapidly into clinical settings and scientific studies are providing mechanisms of action to explain the therapeutic effects.

Probiotics and microbiota

Probiotics such as non-pathogenic microbial feed or food supplements are already being widely studied in the treatment of GI diseases including irritable bowel syndrome, inflammatory bowel disease, sever acute pancreatitis, and chronic liver diseases[63-66]. The use of probiotics in the treatment of GI infections is gaining traction as an alternative or complement to antibiotics due to their potential to decrease the use of antibiotics or reduce their side effects[67]. Results of clinical trials combining the use of agents for first-line eradication and adjunctive probiotics have been reported to increase the *H. pylori* eradication rate[68-70]. Moreover, emerging evidence shows that probiotics attenuate *H. pylori* infection rates and associated inflammation. The results of several *in vitro* studies have shown that *Lactobacillus* can ameliorate *H. pylori*-induced inflammation by modulating cytokine induction, activating suppressor of cytokine signaling (SOCS) expression, and inactivating the JAK2, Smad7 and NF-κB signaling pathways[71-73]. Twelve human studies have investigated the efficacy of combinations of antibiotics and probiotics, whereas 16 studies used probiotics alone as an alternative to antibiotics for the treatment of *H. pylori* infection. Most of the studies showed an improvement of *H. pylori* gastritis and decreases in *H. pylori* colonization after probiotic administration. None of the studies, however, could demonstrate complete eradication of *H. pylori* in-

fection by probiotic treatment[67,74]. It should be noted, however, that one of the well-documented advantages of probiotic combinations was a reduction in adverse effects induced by *H. pylori* eradication treatment[75]. Since long-term intake of products containing probiotic strains may have a favorable effect on *H. pylori* infection in humans, particularly by reducing the risk of developing disorders associated with high degrees of gastric inflammation, it is possible that they contributed ultimately to chemoprevention. Recent advances in high throughput analysis technology have highlighted the importance of probiotics in *H. pylori* infection as well as other GI diseases involving "*microbiota*" as key controllers of *H. pylori* infection. The human organism is colonized by a large number of microorganisms that play important roles in several biochemical reactions. The microorganisms that colonize the human GI tract are collectively described as *microbiota* and a typical human may carry over 40×10^3 bacterial species in the intestinal microbiome[76]. The microbiota of the human stomach and its influence on *H. pylori* colonization has been characterized. Most phylotypes belong to the phyla *Proteobacteria*, *Firmicutes*, *Actinobacteria*, *Bacteroidetes* and *Fusobacteria*. *Lactobacillus* species are acid-resistant and commensal and their concentrations in the normal human stomach vary between 0 and 10^3 mL^{-1}. The human microbiome co-evolved with mankind, is part of human physiology, and contributes to homeostasis. Although microbiota–host interactions through metabolic exchange and co-metabolism of substrates, or metabolome–metabolome interactions are still poorly understood, they may be implicated in the etiology of many human diseases including *H. pylori* infection. Therefore, the advantages attributed to probiotics in *H. pylori* infection, such as augmentation of the eradication rate, attenuation of side effects associated with eradication drugs, and some direct anti-inflammatory action, may represent only a small part of their involvement. Extensive investigation of the *microbiota* relevant to *H. pylori* infection will be required to elucidate additional mechanisms and relationships.

Mesenchymal stem cells

Although gastric epithelial stem cells have been localized, little is known about their molecular biology. Recent reports described the use of inducible Cre recombinase activity to indelibly label candidate stem cells and their progeny in the distal stomach[77]. *H. pylori*-induced chronic inflammation affects differentiation and promotes metaplasias, in which cellular and molecular mechanisms in spasmolytic polypeptide-expressing TFF2 pseudopyloric metaplasia predominates. The identification of signaling pathways and events that take place during embryonic development that eventually establish adult stem cells to maintain the specific features and functions of the stomach mucosa have elucidated how gastric epithelial stem cells contribute to either good regeneration, such as healing or rejuvenation, or bad regeneration, such as carcinogenesis. For example, because bone marrow-derived mesenchymal stem cells [BM-Mesenchymal stem cells (MSCs)] are known to play an important role in *H. pylori*-induced gastric carcinogenesis, Lin *et al*[78] transplanted BM-MSCs into the stomach of mice with a 44 wk mouse-adapted *H. pylori* infection. Study results revealed that transplantation of BM-MSCs into a chronic *H. pylori*-infected mouse led to an immunosuppressive environment such that stem cells fostered an environment compatible with the development of *H. pylori*-induced gastric cancer. Similarly, recent investigations into gastric stem cell or progenitor cell biology have uncovered valuable information for understanding gastric gland renewal and maintenance of homeostasis relevant to *H. pylori* infection. Ding and Zheng[79] provided clues for further defining the mechanisms by which gastric cancer may originate and progress. Using Lgr5, villin-promoter, TFF2-mRNA, and Mist, all of which are factors identified as gastric stem/progenitor cell markers, they explored how *H. pylori* or chronic inflammation affected gastric stem cells or their progenitors which give rise to mucus-, acid-, pepsinogen-, and hormone-secreting cell lineages. From their study results, they concluded that *H. pylori* infection induced oncogenic transformation and propagation into tumors based on the tumor microenvironment. In his recent publication, Peek stated that chronic *H. pylori* infection led to DNA damaged stem cells, a condition which could have severe negative consequences[80]. In detail, *H. pylori*-infected rodents that developed dysplasia harbored a subset of gastric epithelial cells in which levels of spermidine oxidase (SMO) production and DNA damage were high, but which were resistant to apoptosis, thereby representing a cellular population poised for neoplastic transformation targeted for gastric stem cells. In contrast to the results of these harmful interventions using gastric stem cells in *H. pylori*-associated gastric carcinogenesis, we found that exogenous stem cells could provide options for cancer prevention and intervention, as MSCs were able to rejuvenate atrophic gastritis into non-atropic condition and significantly ameliorate *H. pylori*-induced gastritis. Because gastric stem cells can have positive or negative effects dependent upon how they are used, further experimentation will be necessary to advance our understanding of stem cell properties in *H. pylori* infection, as well as the potential for rejuvenation of *H. pylori*-infection-associated chronic atrophic gastritis with or without intestinal metaplasia.

Antioxidants

H. pylori leads to chronic inflammation which in turn leads to oxidative stress derived from immune cells and gastric epithelial cells and is one of the main contributors to DNA damage associated with apoptosis and neoplastic transformation[81]. Both pathogen and host factors contribute directly to oxidative stress, including *H. pylori* virulence factors, and pathways involving DNA damage and repair, polyamine synthesis and metabolism, and oxidative stress responses. As previously mentioned, polyamine oxidation by SMO causes H_2O_2 release, DNA damage and apoptosis, and subsequent gastric transfor-

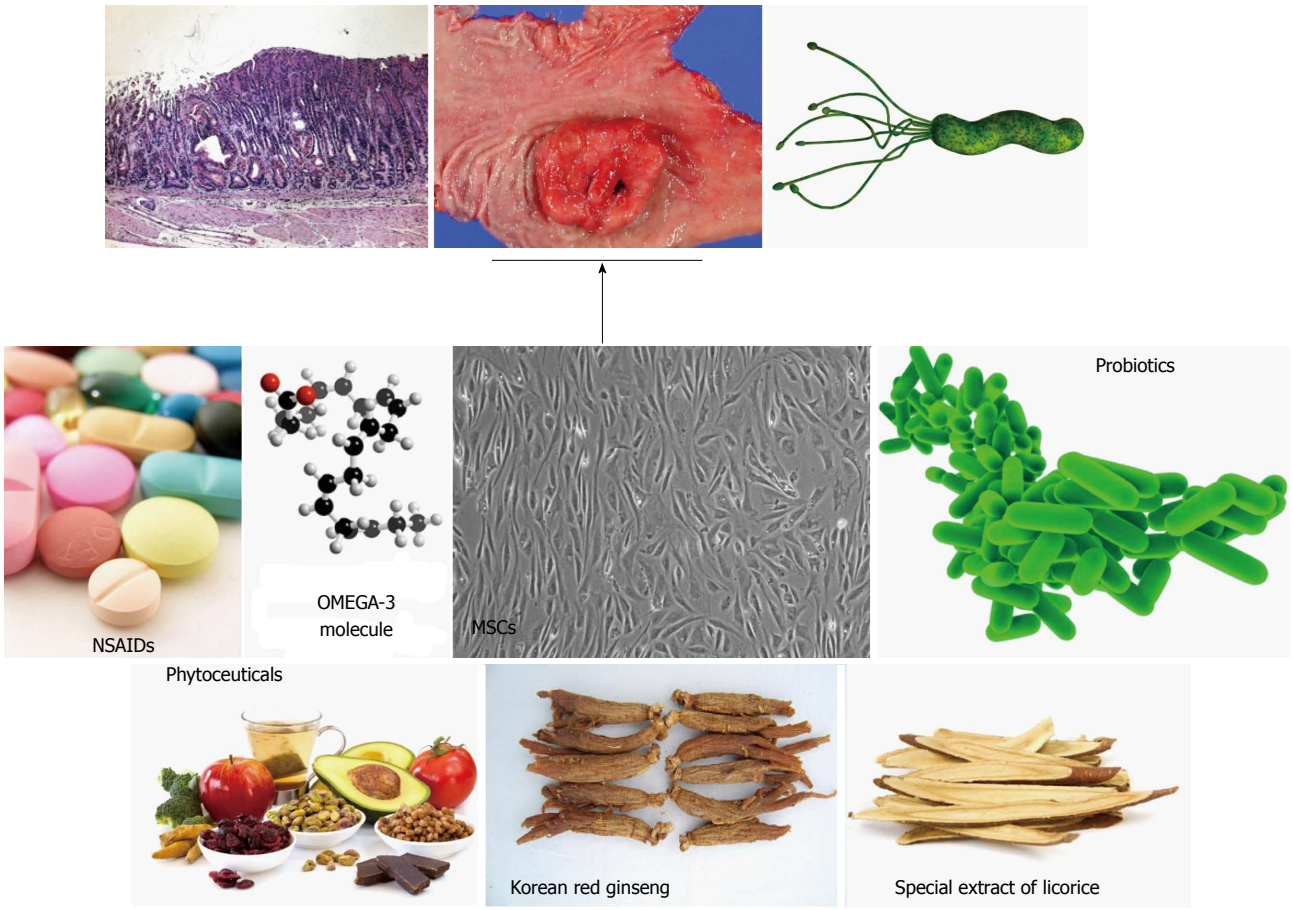

Figure 3 A non-microbial approach for *Helicobacter pylori*-associated gastritis as well as gastric cancer. Simply removing *Helicobacter pylori* (*H. pylori*) can contribute to gastric cancer prevention in some patients. For example, *H. pylori* eradication suppressed the metachronous occurrence of gastric cancer in patients who underwent endoscopic submucosal dissection, whereas insignificant outcomes were noted in general eradication. 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.

mation[82,83]. Since many studies reporting the potential contribution of oxidative stress and chronic inflammation to *H. pylori*-associated gastric carcinogenesis, antioxidants can provide enough hope for cancer prevention. *H. pylori*-associated inflammation can induce DNA damage due to oxygen radicals by persistent inflammatory cell infiltrations in the gastric mucosa, which may lead to alterations of the gene and result in the development of diffuse-type carcinoma. In order to elucidate the influence of *H. pylori* on changes in inflammation-related DNA damage, Hahm *et al*[84] measured the sequential changes of the 8-hydroxydeoxyguanosine (8-OHdG) content of DNA and changes of two biomarkers, inducible nitric oxide synthase (iNOS) and apoptosis, from human gastric mucosa according to the status of *H. pylori*. The increased levels of oxidative DNA damage, increased occurrences of apoptosis, and increased expressions of iNOS seemed to provide the mechanistic links between *H. pylori* infection and gastric carcinogenesis. In a subsequent study, we treated *H. pylori*-associated chronic atrophic gastritis with an antioxidative drug, rebamipide, and found that it contributed to either augmentation of the eradication rate or a significant decrement of 8-OHdG content[85]. Diseases associated with free radical overproduction are provoked by "blazed reactive oxygen species productions" far beyond the host's capacity to quench. Free radicals have been implicated in the pathogenesis of diverse GI diseases including gastroesophageal reflux disease, gastritis, enteritis, colitis, and associated cancers, as well as pancreatitis and liver cirrhosis[86]. Antioxidants administered in a nutritional way or *via* pills will surely contribute to the amelioration of *H. pylori*-associated gastric catcinogenesis. However, additional proof of concept evidence is required.

CONCLUSION

Gastric cancer is a multi-factorial and multi-step disease associated with a variety of risk factors including environmental and pathogenic microbial chronic inflammation. In addition to life-style factors, especially diet, infection with the pathogenic microorganism *H. pylori* is a major concern for gastroenterologists because *H. pylori* infection causes chronic atrophic gastritis and peptic ulcer with an inflammatory response. Unfortunately, modern medicine cannot completely prevent gastric cancer

and even eradication of *H. pylori* is problematic due to expense and antibiotic resistance, as well as insufficient evidence supporting a rationale for eradication. However, the Japanese government decided to take on the great challenge of *H. pylori*-associated chronic gastritis by including its eradication in their guideline this year in an attempt to decrease gastric cancer incidence and mortality. Until such time as proof emerges supporting the concept that *H. pylori* eradication is the fastest means of preventing gastric cancer, the attenuation or intervention of *H. pylori*-induced chronic inflammation may be alternative or complementary methods to achieve the prevention of gastric cancer. As shown in this review, the inhibitors of COX and LOX, a number of natural phytochemicals, including curcumin and broccoli sprouts (sulforaphane), oils such as omgega-3 PUFAs, probiotics, and stem cells have been shown to have anti-inflammatory and antimicrobial activities by targeting small molecules or regulating signaling cascades (Figure 3). Pharmacotherapy and the eradication strategy can provide rapid relief of acute inflammation but cannot correct the underlying cause of chronic inflammation. However, a non-microbial approach for modulating *H. pylori*-associated gastric inflammation may be an attractive and fast way to optimize cancer preventive strategies and minimize adverse side effects associated with therapeutic regimens.

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