

## Efficacy of Cranberry Juice on *Helicobacter pylori* Infection: a Double-Blind, Randomized Placebo-Controlled Trial

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### ABSTRACT

**Background.** *Helicobacter pylori* infection is a major cause of peptic ulcer disease and gastric cancer. This study postulated that cranberry juice would be effective in the suppression of *H. pylori* in an endemically infected population at high risk for gastric cancer.

**Materials and methods.** A prospective, randomized, double-blind, placebo-controlled trial was conducted in Linqu County of Shandong Province, China, where 189 adults aged  $48.9 \pm 11.2$  years (mean  $\pm$  SD) with *H. pylori* infection were randomly divided into two groups: cranberry juice ( $n = 97$ ) and placebo ( $n = 92$ ). Participants were assigned to orally receive two 250-ml juice boxes of cranberry juice or matching placebo beverage daily for 90 days. The degree of *H. pylori* infection was determined using the  $^{13}\text{C}$ -urea breath test before randomization at 35 and 90 days of intervention to assess the efficacy of cranberry juice in alleviating infection.

**Results.** A total of 189 subjects with positive  $^{13}\text{C}$ -urea breath test results prior to randomization completed the study. At day 35 of intervention, 14 of the 97 (14.43%) from the the cranberry juice treatment group and 5 of the 92 (5.44%) of the placebo recipients had negative  $^{13}\text{C}$ -urea breath test results. After 90 days, the study concluded that 14 of the 97 subjects in the cranberry juice treatment group versus 5 of the 92 in the placebo group yielded negative test results. Eleven individuals from the cranberry juice treatment group and only two from the placebo group were negative at 35 and 90 days of experiment. These results are significant ( $p < .05$ ).

**Conclusions.** Regular consumption of cranberry juice can suppress *H. pylori* infection in endemically afflicted populations.

**Keywords.** Intervention, *Helicobacter pylori*, cranberry juice, clinical trial.

*Helicobacter pylori* infection occurs worldwide, but the prevalence rate among adults in developing countries is over 80%, whereas it falls between 20% and 50% in industrialized countries [1]. Accumulated evidence obtained in Linqu County, Shandong Province of China indicates that *H. pylori* infection is associated with an increased risk of developing gastric cancer [2–4], one of the most prevalent diseases in China and internationally [5].

The first line regimen for eradication of *H. pylori* infection currently includes a triple therapy, which combines two known antibiotics with a proton pump inhibitor [6–7]. However, because triple therapy fails to eradicate infection in 10–20% of patients [8], quadruple therapy

was introduced as a new treatment modality as well as rescue treatment for antibiotic-resistant strains of *H. pylori* [9–10]. Although most of these therapeutic modalities are effective, they are usually associated with mild to moderate, or even severe, adverse effects [8–10]. Furthermore, it is very costly and controversial to apply these forms of therapy to populations with endemic *H. pylori* infection. Thus, an alternative mode of treatment, particularly of nontoxic, natural products, that proves more cost-effective and applicable to affected populations without evoking the side effects of antimicrobial treatments, is highly desirable.

It has been suggested that cranberry juice prevents urinary tract bacterial infection in female patients [11–15]. Although the potential mechanisms of action are unclear, in vivo and in vitro studies have illustrated that cranberry juice can help avoid infection by preventing *Escherichia coli* bacteria from adhering to the uroepithelium

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[16]. Bacterial adherence to mucosal cells is the initial step in the development of urinary tract infections. Inhibition of *H. pylori* adhesion to the human gastric mucosa by a high-molecular-weight constituent of cranberry juice was recently demonstrated in vitro [17]. Based on this and other evidence that cranberry juice possesses beneficial health effects, the present randomized, double-blind, placebo-controlled trial was designed and carried out to investigate whether cranberry juice would suppress *H. pylori* in an adult population in Linqu County of Shandong Province. Information regarding the population, gastric cancer deaths, and prevalence of *H. pylori* infection in Linqu County are described in the literature [18–21].

## Methods

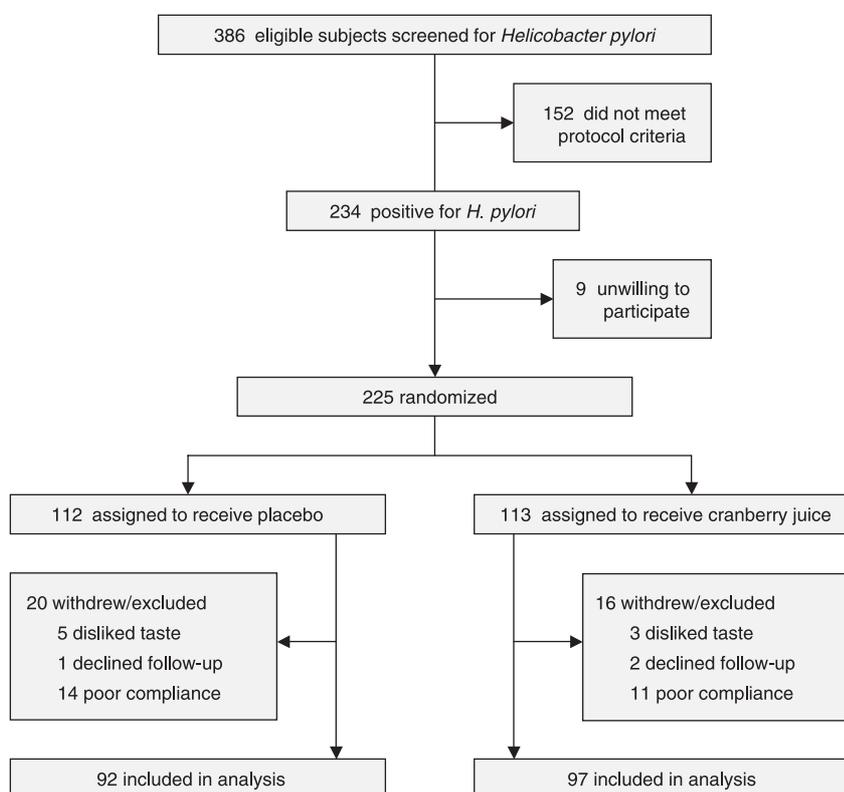
### Study Population

This randomized, double-blind, placebo-controlled trial was conducted in an adult population in Linqu County under the supervision of the faculty from Peking University School of Oncology and in accordance with the principles set forth in the Declaration of Helsinki. The

Institute Review Board (IRB) of the School of Oncology approved the study protocol in April 2002, and the study was completed in December 2002. Three hundred eighty six adults from Linqu County ranging from 26 to 64 years of age were invited to participate in the study. After the names of all participants were transcribed from village population rosters, health officials (Drs L. Zhang and J. Ma) visited each individual to detail the study and offer consent forms to those interested. Individuals who agreed to participate provided signed consent and proceeded to take a  $^{13}\text{C}$ -urea breath test. No current information on the participant's drinking or smoking habits was collected. However, according to a previous case-controlled study of gastric cancer, most residents of Linqu County were tea drinkers, and approximately 81% of the men and 5% of the women were cigarette smokers [18–19]. None of the subjects had received treatment with antibiotics prior to their participation in this study. The flow of participants through this trial is illustrated in Fig. 1.

### Study Protocol

Two hundred fifty-five adult subjects produced positive  $^{13}\text{C}$ -urea breath tests and progressed



**Figure 1** Trial profile.

through the intervention trial. All subjects were randomized to receive 90-day treatment with two 250 ml doses of either cranberry juice or placebo daily. The look-alike placebo beverage contained vitamin C, sugar and natural cranberry flavoring and coloring to simulate the taste of the cranberry juice. Ocean Spray, Inc. [Middleboro, Massachusetts, USA] provided both the cranberry juice and placebo beverage. Trained field staff interviewed all subjects according to a structured questionnaire that included age, sex, address, occupation, previous history of peptic ulcers, and whether any medications, antibiotics, or both were taken during the study. Cases of the beverage were distributed to participants every 12 days. Treatment compliance was confirmed by a daily beverage box count. Dietary information was obtained from the subjects' accomplished questionnaire. To maintain high compliance, staff members from the Peking University School of Oncology visited the participants in their homes and counted the empty boxes every 3–5 days. Empty boxes were collected during each new distribution of beverage supply. Compliance was calculated based on any remaining beverage in the returned packaging. Poor compliance means that the subject did not drink the cranberry juice or placebo continuously in 5 days. The subjects with poor compliance were excluded from the study. All field and laboratory procedures were performed double-blind. Because the  $^{13}\text{C}$ -urea breath test is generally considered to be the gold standard clinical, noninvasive test for detecting active *H. pylori* infection [22–24], it was used in this study to determine the efficacy of this potential treatment modality.

After randomization, *H. pylori* infection status in each subject was evaluated using  $^{13}\text{C}$ -urea breath test at 35 and 90 days of intervention to assess the effectiveness of the treatment. Subjects fasted overnight before undergoing the breath test, and baseline samples of exhaled  $\text{CO}_2$  were collected the following morning. Each subject was then requested to drink 20 ml of water and ingest 80 mg  $^{13}\text{C}$ -urea (> 99%), and their exhaled  $\text{CO}_2$  was collected in sampling tubes 20 and 30 minutes later.  $^{13}\text{CO}_2$  values were determined using gas isotopic ratio mass spectrometer (GIRMS), and any concentration of  $^{13}\text{CO}_2$  at 20 or 30 minutes that exceeded the baseline concentration more than 4 parts per 1000 (> 0.4%) was regarded as positive [23]. In our previous studies, the sensitivity and specificity of this test were 94% and 83%, respectively, in this population [25,26].

### Outcomes and Statistical Analysis

The primary outcome of the study is based on the number of subjects whose initial positive  $^{13}\text{C}$ -urea breath test results were negative at 35 and 90 days study. Sample size calculations were performed before the trial began. Investigators assumed that the overall rate of reduction in *H. pylori* infection that could be attributed to cranberry juice was 20%, with corresponding power ( $\beta$ ) = .80, two-sided  $\alpha$  = .05, and a sample size of 69 subjects in each of the two groups. To account for the possibility of subjects lost to follow-up, the actual sample size power was increased to include 30–40% more subjects than the calculated sample size. Eradication rates of *H. pylori* in the cranberry and placebo groups were compared, and statistical differences were determined using a two-tailed  $\chi^2$  test at  $\alpha$  = .05 with  $df = 1.0$ .

### Role of the Funding Source

Ocean Spray Cranberries, Inc., sponsor of this intervention trial, made the double-blind, placebo-controlled approach possible. They provided the cranberry juice used in the experimental arm of the study and the look-alike beverage that served as placebo.

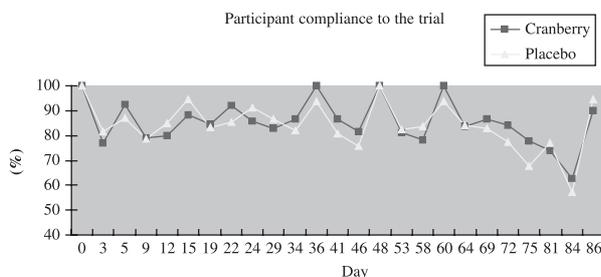
### Results

A total of 225 subjects were initially enrolled in the study, as depicted in the trial profile (Fig. 1). One hundred eighty-nine subjects completed the study, from which 36 withdrew or were excluded because they disliked the taste of the cranberry or placebo beverage and failed to provide sample for the 35- or 90-day  $^{13}\text{C}$ -urea breath test, or had poor compliance during the progress of the study. The data presented are from the 189 subjects who completed the trial and provided initial  $^{13}\text{C}$ -urea breath test values along with values at 35 and 90 days.

Satisfactory treatment balance within strata defined by baseline data was achieved through randomization. Demographic details, including gender, age, and occupation of participants from both groups, are shown in Table 1. Participants' age ranged from 26 to 64 and the trial was balanced accordingly into two groups by gender and occupation as well. There were no differences between the questionnaires presented to the cranberry and the control groups. Figure 2

**Table 1** Demographics of the participants of the study

	Cranberry juice	Placebo
n	97	92
Male	50 (51.5%)	47 (51.1%)
Female	47 (48.5%)	45 (48.9%)
Mean age (SD) in years	48.8 (10.7)	49.1 (11.4)
Farmers	77	69
Residents	20	23

**Figure 2** Profile of the participants' compliance to the trial, both in the cranberry juice treatment group and the control group.

illustrates the compliance of the subjects. Over the 90-day trial, the overall average compliance rate among cranberry treatment and placebo recipients was 85%.

At day 35 and day 90, results of the breath test for *H. pylori* were negative in 14 of the 97 (14.43%) subjects who consumed cranberry juice and five of the 92 (5.44%) who consumed placebo (Table 2). Among 14 negative subjects in the treatment group, 11 subjects were negative at 35 and 90 days, whereas only two of same subjects were negative both at 35 and 90 days from the placebo group. We further calculated the means of delta over baseline values of  $^{13}\text{C}$ -urea breath test at 35 and 90 days from the treatment and placebo groups. Although the means of delta over baseline value was significantly reduced to 1.97 at 90 days as compared with 2.52 before the treatment among 97 subjects in the cranberry group ( $p < .05$ ). However, no statistical difference was found between the values at 35 days (2.11) and 90 days (1.97) in this group. Again, we found the difference of means of delta over baseline value was not statistically significant at 35 days (0.11) and 90 days (0.16) among 11 *H. pylori*-negative subjects from the treatment group.

## Discussion

In Linqu County, a rural area in China with one of the world's highest prevalence rates of gastric cancer, 52% of children aged 3–4 years and 72%

**Table 2** Classification of individuals according to *Helicobacter pylori* status, as measured by the  $^{13}\text{C}$ -urea breath test, and percentage of those who moved from *H. pylori*-positive (Hp+) to negative (Hp-) status

	Cranberry juice				Placebo			
	n	Hp+	Hp-	%	n	Hp+	Hp-	%
Baseline	113	113	0	0	112	112	0	0
$\delta$ (means)		2.52	–			3.23	–	
35th Day	97	83	14	14.43*	92	87	5	5.44
$\delta$ (means)		2.11	0.11			2.96	0.04	
90th Day	97	83	14	14.43*	92	87	5	5.44
$\delta$ (means)		1.97	0.15			2.82	0.17	

\*At both 35 and 90 days, the individuals consuming cranberry juice had a greater chance of moving from an *H. pylori*-positive to -negative (–) than the individuals consuming placebo ( $\chi^2 = 4.23$ ;  $p = .04$ ). The critical value,  $\chi^2_{0.05[1]} = 3.84$ ; since  $\chi^2 > \chi^2_{0.05[1]}$ , the null hypothesis that the  $^{13}\text{C}$ -urea breath test value is independent of juice type was rejected.

$\delta$  = delta over baseline value of  $^{13}\text{C}$ -urea breath test.

of adults are infected with *H. pylori* [27]. In an early factorial trial of three interventions to reduce the progression of precancerous gastric lesions in Linqu, 35 among 1142 subjects receiving a 2-week course treatment with amoxicillin and omeprazole developed rashes, from which six discontinued treatment because of adverse reactions [28]. Through this randomized, double-blind, placebo-controlled study in Linqu, we observed that cranberry juice can retard *H. pylori* infection in humans and may be a promising new form of therapy for worldwide management of this infection that does not induce the side-effects caused by antibiotics. Furthermore, because the prevalence rate of *H. pylori* infection is 72% in the Linqu adult population, the 14% reduction in the infection rate observed in this trial may significantly decrease the spread of infection and risk of gastric cancer, although the mode of transmission of *H. pylori* in humans is yet unknown [29].

Cranberry *Vaccinium macrocarpon* is a natural fruit, and this study is a testimony to what has not been previously reported – that dietary consumption of cranberry juice can partially suppress *H. pylori* infection in humans. Cranberries are native to North America and are extensively cultivated for commercial use in certain states, including Wisconsin, Massachusetts, New Jersey, Oregon, and Washington [26]. Cranberry juice cocktail is considered to be effective in preventing or treating urinary tract infections because of its ability to prevent bacterial adhesion to the lining of the urinary tract. This bacteriostatic property of cranberry juice has been attributed to proanthocyanidins [30]. In addition, it is a

good source of vitamin C, fructose, and bioflavonoids with antioxidant properties, which may also contribute to the bacteriostatic effect of its juice. Recent work by Burger et al. reveals that a high molecular weight constituent of cranberry juice can inhibit *H. pylori* adhesion to the human gastric mucosa in vitro [17,31]. This high molecular weight constituent acts on sialyllactose-specific adhesins of *H. pylori* and may also affect other adhesins such as BabA, a 78-kDa outer membrane protein that binds to the fucosylated Lewis B blood group antigen [32]. Based on animal model studies, BabA is relevant in *H. pylori*-associated diseases and may influence disease severity [33]. The 3'sialyllactose sodium salt, an ant adhesion oligosaccharide compound found in human and bovine milk, was recently used in a double-blind, placebo-controlled clinical study to treat *H. pylori* infection [34]. The ant adhesive therapy was safe and well tolerated, but did not suppress or cure *H. pylori* colonization in humans [34]. In contrast, Xiao and Shi have recently demonstrated that cranberry juice fed to mice infected with *H. pylori* can clear *H. pylori* at a rate of 80%, 24 hours after the treatment, and at an eradication rate of 20%, 4 weeks following treatment [35]. Therefore, the actual mechanism by which cranberry juice affects *H. pylori* colonization and suppression warrants further investigation.

A few studies suggested that vitamin C may play a role in *H. pylori* infection. Park et al. demonstrated that a reversed association between vitamin C levels in whole blood, plasma and gastric juice and the severity of *H. pylori* infection in 452 Korean children [36]. Simon et al. have indicated that higher serum levels of ascorbic acid were associated with a decreased seroprevalence of *H. pylori* and of pathogenic *cag A+* strain of *H. pylori* among White Americans [37]. Furthermore, Jarosz [38] investigated the effects of 5 g of vitamin C daily for 4 weeks in the treatment of *H. pylori* infection among the patients with dyspeptic symptoms and chronic gastritis, their results suggest a 30% eradication of the infection. The preparation of placebo in this study did involve vitamin C, and this may be the reason why five subjects from the placebo group who originally tested positive for *H. pylori* later tested negative. The cranberry juice and placebo contained 37.5 mg/100 ml of vitamin C; therefore, each subject had a daily intake of 188 mg of vitamin C per day, a far lower dose than previously discussed. However, the effects

of cranberry juice may be the result of other phytonutrients present in the juice. Recently, it has been shown that the anthocyanins, proanthocyanidins, and flavonol glycosides in cranberry extract have antiproliferative and synergistic effects on human tumor cell lines [39]. These phytonutrient components of the cranberry and their possible role in *H. pylori* infection require further investigation.

In this clinical trial, the efficacy of cranberry juice on *H. pylori* infection at 35 days was similar to that at 90 days of intervention. However, the density and intensity of bacteria in the gastric mucosa of the <sup>13</sup>C-urea-positive subjects were unknown. A mild degree of *H. pylori* colonization in the gastric mucosa may cause increased sensitivity to cranberry juice treatment because the infection is less extensive and the gastritis is nonatrophic in general [40]. As the effects of cranberry juice cocktail on *H. pylori* infection were already apparent at day 35 of this trial, it is suggested that future intervention studies use this as the outcome endpoint or longer. Furthermore, investigations among selected populations that include children and teenagers are needed to assess the efficacy of cranberry juice in delaying or preventing *H. pylori* infection early in life. We did not study the efficacy of cranberry juice on *H. pylori* infection in children who appear to be more susceptible to the infection than adults [27], but the current results may have implications for prevention of the infection with safety management and preventive measures during childhood. Murry et al. have reported an inverse relationship between alcohol consumption and *H. pylori* infection, in which modest consumption of wine and beer prevents infection presumably through the suppression of the bacterium [41]. On the other hand, smoking and coffee consumption have been found to be unrelated to active *H. pylori* infection [41]. These findings encourage further investigation alongside the necessary studies that are aimed at elucidating the dose-response relationship and mechanisms of action of the phytonutrients present in cranberry juice cocktail.

In conclusion, this is the first human intervention trial, to our knowledge, designed to study the effects of cranberry juice on *H. pylori* infection. The results of this preliminary study in Linqu County suggest that regular consumption of cranberry juice may reduce *H. pylori* infection in adults, which remains an important public health issue worldwide.

This study was supported by a grant from Ocean Spray Cranberries, Inc. The authors thank Dr Joseph Speroni and Daisy Hong from Ocean Spray, Inc. for their excellent technical assistance, and Debra A. Wong from the University of California, Los Angeles for providing editorial support.

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