GASTROENTEROLOGY

Suppression of *Helicobacter pylori* infection by daily cranberry intake: A double-blind, randomized, placebo-controlled trial

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Abstract

Background and aim: Dietary strategies that contribute to reducing incidence of *Helicobacter pylori* infection without negative side effects are highly desirable owing to worldwide bacterial prevalence and carcinogenesis potential. The aim of this study was to determine dosage effect of daily cranberry consumption on *H. pylori* suppression over time in infected adults to assess the potential of this complementary management strategy in a region with high gastric cancer risk and high prevalence of *H. pylori* infection.
Methods: This double-blind, randomized, placebo-controlled trial on 522 *H. pylori*-positive adults evaluated dose–response effects of proanthocyanidin-standardized cranberry juice, cranberry powder, or their placebos on suppression of *H. pylori* at 2 and 8 weeks by ^{13}C-urea breath testing and eradication at 45 days post-intervention.
Results: *H. pylori*-negative rates in placebo, low-proanthocyanidin, medium-proanthocyanidin, and high-proanthocyanidin cranberry juice groups at week 2 were 13.24%, 7.58%, 1.49%, and 13.85% and at week 8 were 7.35%, 7.58%, 4.48%, and 20.00%, respectively. Consumption of high-proanthocyanidin juice twice daily (44 mg proanthocyanidin/240-mL serving) for 8 weeks resulted in decreased *H. pylori* infection rate by 20% as compared with other dosages and placebo ($P < 0.05$). Percentage of *H. pylori*-negative participants increased from 2 to 8 weeks in subjects who consumed 44 mg proanthocyanidin/day juice once or twice daily, showing a statistically significant positive trend over time. Encapsulated cranberry powder doses were not significantly effective at either time point. Overall trial compliance was 94.25%. Cranberry juice and powder were well-tolerated.
Conclusions: Twice-daily consumption of proanthocyanidin-standardized cranberry juice may help potentiate suppression of *H. pylori* infection. Trial registration: ChiCTR1800017522, per WHO ICTRP.

Introduction

Over half the world's population is infected with *Helicobacter pylori*, which can induce peptic ulcer and increase risk of developing gastric cancer (GC).[1–3] Among the Asian countries, China has one of the highest incidences of GC.[4] *H. pylori* screening followed by conventional triple or quadruple antibiotic treatment is effective in preventing GC[5–12]; however, treatment failure rates of 10–30%, significant antibiotic resistance development, and other barriers to antibiotic treatment including cost, availability, and potential side effects have left infected individuals at an increased risk for

future GC development.[2,13,14] Complimentary strategies with fewer negative side effects are needed that could contribute to partial suppression of *H. pylori* infections within populations, potentially helping to reduce overuse of antibiotics. While not alternatives to antibiotics, certain dietary interventions have shown bacterial suppression effects, reducing overall disease incidence without total pathogen eradication.[15,16] There is increased interest in implementing food-based regimens that are culturally acceptable, affordable, and well tolerated and help maintain microbiome diversity, which can benefit overall health.[17]

The majority of studies on dietary components and suppression of *H. pylori* have been *in vitro*, with few clinical studies on colonized individuals.[17] Cranberry (*Vaccinium macrocarpon* Ait.) is a fruit that has been shown clinically to suppress infections when consumed regularly.[18,19] A double-blind randomized, placebo-controlled trial (RCT) of 189 *H. pylori*-positive individuals in China in 2005 found a significant 14.3% decrease in the *H. pylori* infection rate at both 35 and 90 days in participants who consumed two daily servings of 250 mL of cranberry juice (27%).[18] An RCT in Chile on 295 *H. pylori*-positive children found suppression rates of 16.9% after 200 mL of cranberry juice daily intake over a 3-week period.[19] *H. pylori*-infected mice administered with cranberry juice (0.5 mL/mouse) had a significant 80% bacterial suppression after 24 h and a 20% eradication rate after 4 weeks.[20] Eradication sustainability was low 1 month after cranberry interventions ceased,[19,20] indicating that regular consumption may be necessary to maintain suppression.

Mechanisms of action of cranberry in suppression of *H. pylori* may be due to phenolic compounds found in the fruit, especially the complex oligomeric A-type proanthocyanidins (PACs) that have been implicated in prevention of adhesion of *Escherichia coli* to bladder cells[21] and oral bacteria to tooth surfaces.[22] This bacterial anti-adhesion effect decreases infection but is not bactericidal, therefore reducing the potential for proliferation of resistant bacterial strains.[23] *In vitro* studies in Israel demonstrated that a cranberry extract containing predominantly PACs prevented adhesion of *H. pylori* sialic acid-specific strains to human gastric mucus and stomach cells.[24,25] A polyphenolic fraction of cranberry inhibited growth of two *H. pylori* strains in a dose-dependent manner, causing morphological changes in the bacteria that prevented replication.[26]

Cranberry products utilized in these previous studies were not standardized for PAC content, and single clinical doses were arbitrarily determined, making it difficult to recommend effective dietary intervention strategies using cranberry. Determining dose–response, frequency of dosing, and active cranberry product forms that improve *H. pylori*-negative rates is needed to develop this complementary approach to increasing bacterial suppression in susceptible populations. Thus, an RCT was designed and carried out in Linqu County, Shandong Province in China, which has one of the highest GC mortality rates worldwide and high prevalence of *H. pylori* infection,[13] to determine the daily dosage of PAC in cranberry juice and juice-derived powder required to suppress *H. pylori* at 2 and 8 weeks following once-daily or twice-daily consumption.

Methods

Study design. The study intervention phase was an RCT, designed to assess the dose–response effects at 2 and 8 weeks of daily consumption of either cranberry juice or juice-based powder standardized by PAC dosage or matching placebos on suppression of *H. pylori*. Additional testing was done to determine if bacterial suppression was sustained 45 days after completion of the intervention phase. The study was conducted in Linqu County, between August 2018 and April 2019, by researchers from Peking University Cancer Hospital & Institute (PUCHI), China. The study was approved by the institutional review board of PUCHI and was

registered as ChiCTR1800017522 in accordance with World Health Organization International Clinical Trials Registry Platform requirements prior to execution of the study. Standard triple therapy with proton pump inhibitors and antibiotics was provided to subjects who remained *H. pylori* positive at the conclusion of the trial. Written informed consent was obtained from all subjects.

Study population. The ^{13}C-urea breath tests (^{13}C-UBT) conducted between August and December 2018 identified 1017 eligible subjects from 21 communities in Linqu County. A total of 525 *H. pylori*-positive adults, aged 18–60 years, met the recruitment criteria and were invited to participate in the trial. Given the 5% initial eradication for the placebo and 20% for active, the smallest sample size of 67 subjects in each group was required to reach the power $(1 - \beta)$ of 0.80 with the significant level (α) at 0.05.

Informed consent for participation was obtained from each subject; it was explicitly explained by trained interviewers that *H. pylori*-positive residents would be assigned into a high-dose, low-dose, or placebo group; they would be free to terminate enrollment and leave the study at any time; and they had a right to receive any medical care. A structured questionnaire was used at baseline requesting information on demographic characteristics, family history of cancer, personal history of major diseases, and lifestyle factors. Eligible subjects were allowed to taste cranberry juice to determine palatability and asked if they are able to swallow capsules. As an incentive to participate, subjects were informed that they would receive standard triple therapy antibiotic treatments at the conclusion of the study if they were *H. pylori* positive following the trial.

Residents with any medical history of peptic ulcer or reported upper abdominal symptoms including pain, burning sensation, acidic taste in the mouth, and unpleasant regurgitation of stomach contents were excluded as suspected cases of ulcerous disease. In addition, subjects with the following conditions were also excluded from the trial: serious medical conditions, undergoing active cancer treatment, currently or previously on antibiotic therapy for *H. pylori* infection, history of congestive heart failure, respiratory failure, stroke, seizures, pregnancy, and mental or psychiatric illness.

Participants were provided with a written information sheet to report any potential adverse events during the study. In addition, participants would be withdrawn from the study within 24 h of any episodes of ulcer, perforation, upper gastrointestinal bleeding or any moderate or severe adverse events.

Investigational products. Cranberry juice concentrate (50° Brix), pH 2.69, titratable acidity 10.1 (wt/wt) as citric, derived from USA-sourced berries and press extracted to enhance and preserve PAC/polyphenol levels, was formulated into two standardized investigational product beverages. One formulation contained 17.5% cranberry juice (2.282% cranberry concentrate, 5.91% beet sugar, and 91.81% water), and the second formulation contained 35% cranberry juice (4.563% cranberry concentrate, 11.81% beet sugar, and 83.62% water). Juices were hot filled into 240-mL polyethylene terephthalate bottles to pasteurize contents and produce shelf-stability at room temperatures. Placebo beverage that did not contain active cranberry constituents but was cranberry flavored was provided by Ocean Spray Cranberries Inc.,

Middleboro, MA, USA. The standardized cranberry powder derived from cranberry juice extract was mixed with excipients (mannitol [Pearlitol 160C], silica colloidal anhydrous, and magnesium stearate) at a ratio of 77.7% cranberry powder to 22.3% excipients, and 280 mg was packaged in each red opaque gelatin capsule. The equivalent amount of placebo powder consisting of excipient ingredients was packaged in identical capsules. Phenolic component analyses of the finished investigational products were

performed by Complete Phytochemical Solutions, LLC, Cambridge, WI, USA; and results are presented in Table S1.

Randomization and blinding. A total of 525 *H. pylori*-positive subjects from 21 communities (divided into two blocks) were initially enrolled; three refused to receive the intervention and were excluded before randomization. Consequently, a total

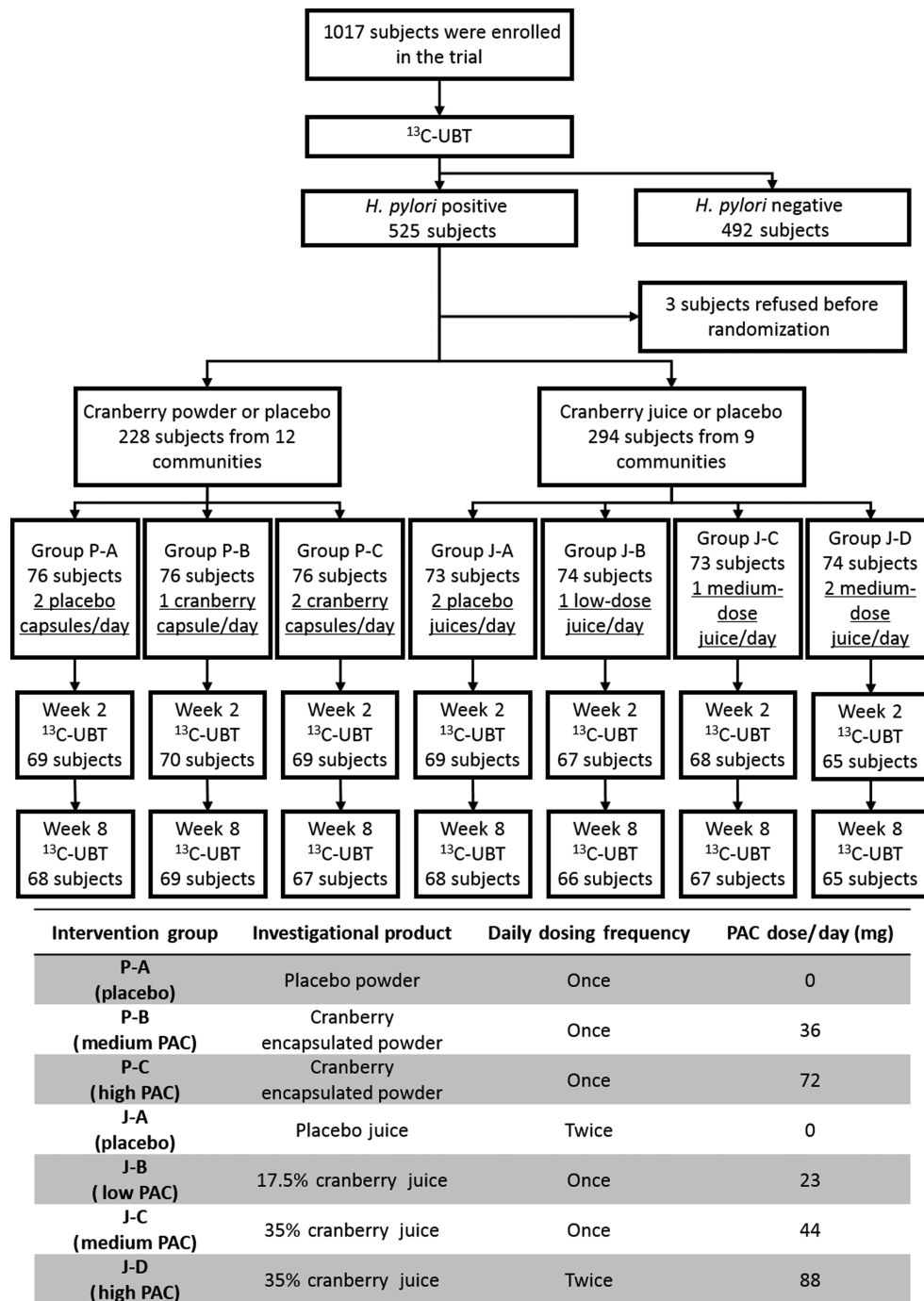| Intervention group	Investigational product	Daily dosing frequency	PAC dose/day (mg)
P-A (placebo)	Placebo powder	Once	0
P-B (medium PAC)	Cranberry encapsulated powder	Once	36
P-C (high PAC)	Cranberry encapsulated powder	Once	72
J-A (placebo)	Placebo juice	Twice	0
J-B (low PAC)	17.5% cranberry juice	Once	23
J-C (medium PAC)	35% cranberry juice	Once	44
J-D (high PAC)	35% cranberry juice	Twice	88

FIGURE 1   Participant flow diagram with intervention dosing scheme.

of 522 subjects were allocated into the juice arm or encapsulated powder arm at random by block and then were assigned to seven intervention groups by individual randomization via computer (Fig. 1). Briefly, 294 subjects living in nine communities were assigned into one of four intervention groups (placebo, low-PAC, medium-PAC, or high-PAC dose) of the juice arm (73 or 74 subjects for each group), and 228 subjects from 12 communities were assigned into one of three intervention groups (placebo, medium-PAC, or high-PAC dose) of the encapsulated powder arm (76 subjects for each group). Within the two arms of the trial (juice and encapsulated powder), dose–response effects on *H. pylori* suppression were evaluated based on PAC dose.

Seven codes indicating different types and dosages of the intervention products were generated by an independent statistician and were sealed in an envelope until the end of the trial. Both the participants and the investigators were masked to treatment assignment to preserve double-blinding.

Interventions. The *H. pylori*-positive subjects received an 8-week supply of cranberry juice, encapsulated powder or matching placebos at the initiation of the trial (week 0), instructions for use of products, and subject food records and treatment diaries to record daily product use, dietary intake, changes in concomitant therapies, and any adverse events and symptoms throughout the study. To maintain double-blinding, coded intervention products were packaged individually for each participant in eight boxes, each containing a 1-week supply, labeled with the identity code of each participant, and delivered by research staff members. For the juice arm, PAC-standardized, shelf-stable bottled cranberry beverage (240-mL serving) or a matching placebo were provided and either refrigerated or stored by participants at room temperature (out of the sun) for the duration of the trial. For the encapsulated powder arm, PAC-standardized cranberry juice-based powder (280-mg servings in capsules) or a matching placebo were provided and stored at room temperature. Specifically, subjects in each intervention group received investigational products containing standardized PAC dosages and dosing instructions according to the scheme illustrated in Figure 1.

Over the 8-week intervention period, subjects in the low-PAC group (group J-B) consumed one bottle (240 mL) of cranberry juice daily containing 23 mg PAC/bottle, while subjects in the medium-PAC group (group J-C) consumed one 240-mL bottle containing 44 mg PAC. Subjects in the high-PAC group (group J-D) consumed two 240-mL bottles of juice (44 mg PAC/bottle) daily, every morning and evening. Subjects in the encapsulated powder arm swallowed one (group P-B) or two (group P-C) 280-mg capsule(s) of cranberry powder, which contained 36 mg PAC/capsule or two placebo capsules (group P-A) daily in the morning over the 8-week intervention period.

To measure compliance, staff members of PUCHI counted empty product containers and discussed any adverse events at weeks 2 and 8 of the intervention. A subject was considered to have poor compliance with the intervention and subsequently excluded from the per-protocol analysis in the following situations: (i) missed more than 5% of the investigational product doses over the entire intervention period, or (ii) continually missed three doses of the investigational product, or (iii) missed the staff interview at week 2 and/or week 8.

Measurement of Helicobacter pylori infection. All subjects were given a ^{13}C-UBT at baseline to determine initial infection status and again at weeks 2 and 8 to test effectiveness of the investigational products. Subjects who tested negative at 8 weeks were retested 45 days later, after the investigational products stopped being administered, to determine *H. pylori* eradication rate. Details of the ^{13}C-UBT were described in previous publications.[13]

Statistical analyses. The primary outcome variable was the *H. pylori*-negative rate in the cranberry and placebo groups after 2 and 8 weeks, which was analyzed by both intention-to-treat (ITT) and per-protocol strategies. Statistical differences were determined using a two-tailed χ^2 test or Fisher's exact conditional test at $\alpha = 0.05$. Odds ratios and corresponding 95% confidence intervals were calculated by multivariable unconditional logistic regression to evaluate the potential factors (age, gender, tobacco smoking, alcohol consumption, or baseline body mass index [BMI]) influencing *H. pylori*-negative rates at week 8. Statistical analyses and randomization were conducted by Statistical Analysis System software (version 9.2; SAS Institute, Cary, NC).

Results

The mean age of the 522 subjects was 47.24 ± 11.53 years, and 232 subjects were male (44.40%). No statistical difference was found in age, gender, tobacco smoking, alcohol consumption, or baseline BMI between intervention groups either in the juice arm or the encapsulated powder arm, ensured by the randomization of the trial participants (Table 1).

Following the 8-week intervention, 492 out of 522 subjects completed the treatment (compliance 94.25%), of which 477 (compliance 96.95%) received the second ^{13}C-UBT (week 2) and 470 (compliance 95.53%) received ^{13}C-UBT both at week 2 and week 8 (Fig. 1). No severe side effects or life-threatening events were observed among all subjects within the intervention period.

Effect of cranberry juice on Helicobacter pylori suppression at weeks 2 and 8. Of the 294 subjects receiving cranberry juice intervention or placebo, ^{13}C-UBT data were successfully collected on 266 subjects at both weeks 2 and 8. ITT analysis including all 294 subjects revealed *H. pylori*-negative rates at week 2 of 13.70% (10/73), 6.67% (5/74), 1.37% (1/73), and 12.16% (9/74) in J-A (placebo), J-B (low-PAC), J-C (medium-PAC), and J-D (high-PAC) groups, respectively, with statistically significant difference across four groups ($P = 0.028$). Further analysis found the *H. pylori*-negative rate in high-PAC group was significantly higher than that of the medium-PAC group ($P = 0.009$). No statistical difference was found between high-PAC with placebo or low-PAC groups. Per-protocol analysis including the 266 subjects with ^{13}C-UBT data at both weeks 2 and 8 found that *H. pylori*-negative rates at week 2 were 13.24% (9/68), 7.58% (5/66), 1.49% (1/67), and 13.85% (9/65) in placebo, low-PAC, medium-PAC, and high-PAC groups, respectively, with statistically significant difference across four groups ($P = 0.041$). The rate in high-PAC group was significantly higher than in

Table 1 Selected characteristics of subjects in each group by intervention product arms

Characteristics	Juice arm					Encapsulated powder arm			
	Group J-A (n = 73)	Group J-B (n = 74)	Group J-C (n = 73)	Group J-D (n = 74)	P	Group P-A (n = 76)	Group P-B (n = 76)	Group P-C (n = 76)	P
Age, mean ± SD	48.07 ± 9.31	45.76 ± 11.43	47.42 ± 11.91	47.64 ± 10.63	0.590[†]	46.26 ± 11.88	45.8 ± 12.40	49.72 ± 12.61	0.102[†]
Sex, *n* (%)					0.482[‡]				0.983[‡]
Male	33 (45.21)	26 (35.14)	26 (35.62)	32 (43.24)		38 (50.00)	39 (51.32)	38 (50.00)	
Female	40 (54.79)	48 (64.86)	47 (64.38)	42 (56.76)		38 (50.00)	37 (48.68)	38 (50.00)	
Smoking, *n* (%)					0.666[‡]				0.921[‡]
No	56 (76.71)	59 (79.73)	59 (80.82)	54 (72.97)		52 (68.42)	52 (68.42)	54 (71.05)	
Yes	17 (23.29)	15 (20.27)	14 (19.18)	20 (27.03)		24 (31.68)	24 (31.68)	22 (28.95)	
Drinking, *n* (%)					0.223				0.286[‡]
No	49 (67.12)	54 (72.97)	57 (78.08)	60 (81.08)		42 (55.26)	49 (64.47)	51 (67.11)	
Yes	24 (32.88)	20 (27.03)	16 (21.92)	14 (18.92)		34 (44.74)	27 (35.53)	25 (32.89)	
BMI, mean ± SD	24.54 ± 2.74	23.53 ± 3.57	24.32 ± 2.88	24.06 ± 2.29	0.179[†]	24.65 ± 3.03	23.70 ± .56	24.32 ± 2.75	0.161[†]

[†]One-way ANOVA.
[‡]Chi-square test.
J-A, placebo juice; J-B, low-proanthocyanidin (PAC) juice; J-C, medium-PAC juice; J-D, high-PAC juice; P-A, placebo encapsulated powder; P-B, medium-PAC encapsulated powder; P-C, high-PAC encapsulated powder.

medium-PAC group (*P* = 0.007); however, no statistical difference was observed between high-PAC group and placebo.

For the long-term effect after 8 weeks, ITT analysis found the *H. pylori*-negative rates were 6.85% (5/73), 6.67% (5/74), 4.11% (3/73), and 17.57% (13/74) in placebo, low-PAC, medium-PAC, and high-PAC groups, respectively, with a *P* value of 0.012. Further inter-group analysis found the *H. pylori*-negative rate was significantly higher in high-PAC group than in the other three groups (*P* < 0.05). In pre-protocol analysis, *H. pylori*-negative rates were 7.35%, 7.58%, 4.48%, and 20.00%, respectively (*P* = 0.012). The rate was significantly higher in high-PAC group than in the other three groups (*P* < 0.05) (Table 2).

Effect of cranberry powder on Helicobacter pylori suppression at weeks 2 and 8.
Of the 228 subjects receiving cranberry powder intervention or placebo, ^{13}C-UBT data were successfully collected on 204 subjects at both weeks 2 and 8. In ITT analysis including all 228 participants, subjects without second or third ^{13}C-UBT data were considered *H. pylori*-positive.

H. pylori-negative rates at week 2 were 10.53% (8/76), 10.53% (8/76), and 9.21% (7/76) in groups P-A (placebo), P-B (medium-PAC), and P-C (high-PAC), respectively, which did not show statistically significant difference across comparison groups (*P* = 0.953). Per-protocol analysis of the 204 subjects with ^{13}C-UBT data at both weeks 2 and 8 found suppression rates at week 2 were 11.67% (8/68), 11.59% (8/69), and 10.45% (7/67), respectively, without statistical significance (*P* = 0.966).

At week 8, suppression rates were 11.84% (9/76), 6.58% (5/76), and 7.89% (6/76) in placebo, medium-PAC, and high-PAC powder groups, respectively, yet no statistical differences were observed (*P* = 0.490) by ITT analysis. In pre-protocol analysis, suppression rates were 13.24% (9/68), 7.25% (5/69), and 8.96% (6/67), respectively, without statistical differences (*P* = 0.479) (Table 3).

Temporal trends of Helicobacter pylori suppression rates in each active intervention group.
We further investigated the temporal trends of *H. pylori* suppression rates over the entire intervention period in each active group in the

Table 2 Effect of cranberry juice on *Helicobacter pylori* suppression at weeks 2 and 8

H. pylori status	Intention-to-treat analysis					Per-protocol analysis				
	Group J-A (n = 73)	Group J-B (n = 74)	Group J-C (n = 73)	Group J-D (n = 74)	P[†]	Group J-A (n = 68)	Group J-B (n = 66)	Group J-C (n = 67)	Group J-D (n = 65)	P[†]
Week 2					0.028					0.041
Negative	10 (13.70)	5 (6.76)	1 (1.37)	9 (12.16)		9 (13.24)	5 (7.58)	1 (1.49)	9 (13.85)	
Positive	63 (86.30)	69 (93.24)	72 (98.63)	65 (87.84)		59 (86.76)	61 (92.42)	66 (98.51)	56 (86.15)	
Week 8					0.021					0.012
Negative	5 (6.85)	5 (6.76)	3 (4.11)	13 (17.57)		5 (7.35)	5 (7.58)	3 (4.48)	13 (20.00)	
Positive	68 (93.15)	69 (93.24)	70 (95.89)	61 (82.43)		63 (92.65)	61 (92.42)	64 (95.52)	52 (80.00)	

[†]Chi-square test.
J-A, placebo juice; J-B, low-proanthocyanidin (PAC) juice; J-C, medium-PAC juice; J-D, high-PAC juice.

Table 3 Effect of cranberry encapsulated powder on *Helicobacter pylori* suppression at weeks 2 and 8

H. pylori status	Intention-to-treat analysis				Per-protocol analysis			
	Group P-A (*n* = 76)	Group P-B (*n* = 76)	Group P-C (*n* = 76)	$P^{\dagger}$	Group P-A (*n* = 68)	Group P-B (*n* = 69)	Group P-C (*n* = 67)	$P^{\dagger}$
Week 2				0.953				0.966
Negative	8 (10.53)	8 (10.53)	7 (9.21)		8 (11.76)	8 (11.59)	7 (10.45)	
Positive	68 (89.47)	68 (89.47)	69 (90.79)		60 (88.24)	61 (88.41)	60 (89.55)	
Week 8				0.490				0.479
Negative	9 (11.84)	5 (6.58)	6 (7.89)		9 (13.24)	5 (7.25)	6 (8.96)	
Positive	67 (88.16)	71 (93.42)	70 (92.11)		59 (86.76)	64 (92.75)	61 (91.04)	

†Chi-square test.

P-A, placebo encapsulated powder; P-B, medium-proanthocyanidin (PAC) encapsulated powder; P-C, high-PAC encapsulated powder.

per-protocol datasets. Subjects in the cranberry juice arm receiving the dose of 44 mg/day PAC (group J-C) exhibited an increasing trend of the *H. pylori*-negative rate from 1.49% to 4.48% from week 2 to week 8 with statistical significance (P for trend = 0.045). Similarly, the *H. pylori*-negative rate significantly increased from 13.85% at week 2 to 20.00% at week 8 for high-PAC juice group (J-D) receiving 44 mg PAC/bottle twice daily (P for trend = 0.001). No statistical temporal trend was found in subjects who received the low-dose intervention (group J-B) over time (P for trend = 0.334) (Fig. 2a).

For the cranberry powder arm, subjects in both the medium-PAC group (P-B) and the high-PAC group (P-C) showed decreased trends of *H. pylori*-negative rates at week 8 compared with week 2. The *H. pylori*-negative rate in group P-C decreased from 10.45% at week 2 to 8.96% at week 8 with statistical significance (P for trend = 0.001) (Fig. 2b).

Factors associated with Helicobacter pylori suppression at week 8.

We further evaluated the factors influencing the suppression of *H. pylori* at week 8 in the per-protocol subjects from both the juice and encapsulated powder arms. Multivariable unconditional logistic regression adjusted for age and intervention group found that in the cranberry juice arm,

female gender, tobacco smoking, alcohol consumption, and BMI were associated with failure of *H. pylori* suppression; however, owing to the limited number of *H. pylori*-negative subjects, the regression model was not robust, and only the female gender gained statistical significance with an odds ratio of 4.54 (95% confidence interval: 1.51–13.65). For the encapsulated powder arm, no statistical association of these characteristics was found with the suppression rate of *H. pylori* (Table 4).

Post-intervention Helicobacter pylori infection status.

H. pylori status was tested 45 days after the intervention phase utilizing ^{13}C-UBT to determine eradication rates of subjects in the seven intervention groups that remained *H. pylori* negative at both weeks 2 and 8. A total of 23 subjects were sustainably *H. pylori* negative during the intervention period, including 12 from the juice arm and 11 from the encapsulated powder arm. Testing revealed that 75% (6/8) of the subjects who received active treatments in the juice arm and 66.7% (4/6) in the encapsulated powder arm remained *H. pylori* negative, whereas 50% (2/4) and 60% (3/5) remained negative in the placebo juice and powder groups, respectively. Owing to limited sample sizes, statistical analyses were not performed (see Table S2).
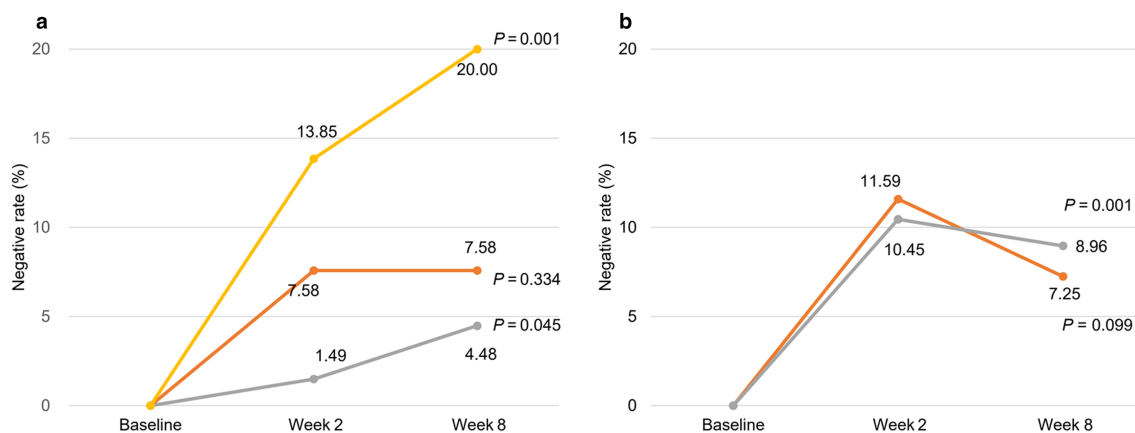

FIGURE 2 Temporal trends of *Helicobacter pylori* suppression rates in each active intervention group in the per-protocol datasets. (a) Juice arm. ━●━, J-B; ━●━, J-C; ━●━, J-D. (b) Powder arm. ; ━●━, P-B; ━●━, P-C. *Temporal trends were determined by Fisher's exact test. [Color figure can be viewed at wileyonlinelibrary.com]

Table 4 Multivariable logistic regression analysis for factors associated with *Helicobacter pylori* suppression at week 8 in per-protocol subjects

Variables	*H. pylori* status in juice arm at week 8			*H. pylori* status in encapsulated powder arm at week 8		
	Negative/positive	OR (95% CI)[†]	*P*[†]	Negative/positive	OR (95% CI)[†]	*P*[†]
Sex						
Male	14/90	1.00		10/95	1.00	
Female	12/150	4.54 (1.51–13.65)	0.007	10/89	0.53 (0.12–2.34)	0.400
Smoking						
No	21/185	1.00		13/127	1.00	
Yes	5/55	3.41 (0.97–11.80)	0.052	7/57	0.83 (0.21–3.40)	0.800
Drinking						
No	20/178	1.00		10/113	1.00	
Yes	6/62	1.84 (0.57–5.92)	0.305	10/71	0.45 (0.12–1.66)	0.232
BMI	26/240	1.03 (0.89–1.19)	0.701	20/184	1.09 (0.95–1.26)	0.235

[†]Unconditional logistic regression adjusted for age and intervention group, with sex, smoking, drinking, and BMI as initial variables entered into the model, where age and BMI were treated as continuous variables.
BMI, body mass index; CI, confidence interval; OR, odds ratio.

Discussion

This RCT determined details on efficacious cranberry product specifications, PAC doses, and frequency of consumption, which resulted in the highest statistically significant *H. pylori* suppression rate of 20% when compared with that of previous trials that used single doses of non-standardized cranberry juices. Improvement in bacterial suppression rate in this trial may be due to a higher PAC dosage in the cranberry juice (44 mg/240-mL serving), greater dosing frequency (twice daily for 8 weeks) potentially resulting in greater and more continuous contact time of the PACs in the gastric lumen, and improved bacterial anti-adhesion effects in the gastric epithelium. *H. pylori* suppression rates were not significantly higher after 2 weeks on cranberry juice; however, the percentage of *H. pylori*-negative participants increased from 2 to 8 weeks in a significant positive trend when juice doses containing at least 44 mg PAC/day and above were consumed, suggesting that daily dosing for longer than 8 weeks could result in even higher suppression rates in future studies.

The ineffectiveness of the cranberry powder in this trial may be due to sub-efficacious dosages and dissolution issues. The powder was derived directly from the juice and contained similar components, but the maximum daily dose of PAC administered was less than the effective juice dose (72 mg PAC/day for the powder *vs* 88 mg PAC/day for the juice). Twice-daily administration may be needed with at least 44 mg PAC per serving. It was not possible to determine if the encapsulated powder fully dissolved in the stomach or in the intestines, confounding its overall bioactive potential. Slow dissolution may have been overcome by dissolving the powder in liquid prior to administration to improve coating of the stomach cavity and interaction with *H. pylori*. Cranberry powder has some advantages over juice in implementing population-based preventative practices, such as storage, portability, and product stability, making it potentially more feasible and acceptable. Future studies could incorporate methods that would fully solubilize juice-based cranberry powder, potentially offering an additional means of consuming cranberry for *H. pylori* suppression.

The status of *H. pylori* infection measured 45 days after the intervention phase indicated that a higher percentage of participants in both the active juice and encapsulated powder arms remained *H. pylori*-free than those in both placebo arms. Even though statistical analyses could not be performed owing to limited sample sizes, these preliminary results suggest that daily cranberry consumption at the proper doses for at least 8 weeks might provide a measure of sustained suppression even if cranberry consumption is terminated. Dietary cranberry PACs are known to induce sustained changes in gut microbiota composition and functionality,[27,28] potentially creating less favorable conditions for *H. pylori* survival even when cranberry is no longer being administered. And research indicates that some resident microbes may inhibit *H. pylori* growth,[29] but further research is necessary to determine if growth of these inhibitory bacterial species is favored by cranberry consumption. There were subjects who remained *H. pylori* negative in the placebo group at the 45-day time point, suggesting the possibility that some other unaccounted dietary component with *H. pylori* inhibitory activity may have been consumed. Studies considering more potential influencing factors and with longer follow-up period after stopping the cranberry usage are warranted.

The data determined in this trial on cranberry products and dosing will be useful for designing future studies to improve outcomes when cranberry is administered with antibiotics for *H. pylori* eradication. In previous studies, cranberry juice (250 mL), administered in conjunction with antibiotic triple therapies, significantly improved *H. pylori* eradication rates in Israeli women than did triple therapy alone.[30] Preventing adhesion to the gastric mucosa may leave non-adherent bacteria more susceptible to the antibiotics. In another study, higher concentrations of antibiotics were needed to kill adherent bacteria.[31] In an RCT of 200 participants in Iran, *H. pylori* eradication rates measured 6 weeks after the intervention were significantly higher when 500 mg of cranberry powder combined with antibiotic triple therapy taken for 2 weeks was compared with triple therapy alone.[32] In situations where antibiotic treatment of *H. pylori* is warranted but resistance to antibiotics is reducing *H. pylori* eradication rates, concurrent administration of cranberry might help improve treatment outcomes.

In conclusion, this study provides additional justification for the utilization of cranberry juice as part of a complementary dietary

approach to *H. pylori* management. Compliance was high, suggesting that participants liked the taste, and they consumed the juice regularly without side effects or other health risks. Cranberry PACs do not appreciably degrade under the highly acidic conditions in the stomach,[33] allowing them to maintain bioactivity. And, polyphenols in cranberry also decrease viability of GC cell lines,[34] inhibit GC *in vivo*,[35] and reduce esophageal adenocarcinoma,[36] offering further potential benefits. Results of the current study suggest that regular consumption of cranberry juice, when administered at the correct dosage and frequency, has potential to partially suppress *H. pylori*, especially in China where endemic infection and GC rates are high.[13] A suppression rate of 20% within a population as demonstrated in this trial could contribute to reducing overall prevalence of *H. pylori* by reducing inoculum levels.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Values of proanthocyanidin, total phenolics, anthocyanins and flavonols in cranberry and placebo investigational finished products.

Table S2. *H. pylori* infection status 45 days after the intervention in subjects sustainedly negative at both weeks 2 and 8.