Modulation of *Helicobacter pylori* colonization with cranberry juice and *Lactobacillus johnsonii* La1 in children

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Abstract

Objective: Probiotics and cranberry have been shown to inhibit *Helicobacter pylori in vitro* owing to bacteriocin production and high levels of proanthocyanidins, respectively. These effects have been confirmed in clinical trials with *H. pylori*–positive subjects. The aim of this study was to evaluate whether regular intake of cranberry juice and the probiotic *Lactobacillus johnsonii* La1 (La1) may result in an additive or synergistic inhibition of *H. pylori* in colonized children.

Methods: A multicentric, randomized, controlled, double-blind trial was carried out in 295 asymptomatic children (6–16 y of age) who tested positive for *H. pylori* by ^{13}C-urea breath test (UBT). Subjects were allocated in four groups: cranberry juice/La1 (CB/La1), placebo juice/La1 (La1), cranberry juice/heat-killed La1 (CB), and placebo juice/heat-killed La1 (control). Cranberry juice (200 mL) and La1 product (80 mL) were given daily for 3 wk, after which a second UBT was carried out. A third UBT was done after a 1-mo washout in those children who tested negative in the second UBT.

Results: Two hundred seventy-one children completed the treatment period (dropout 8.1%). *Helicobacter pylori* eradication rates significantly differed in the four groups: 1.5% in the control group compared with 14.9%, 16.9%, and 22.9% in the La1, CB, and CB/La1 groups, respectively ($P < 0.01$); the latter group showed a slight but not significant increase when compared with the other treated groups. The third UBT was carried out only in 19 of the 38 children who tested negative in the second UBT and *H. pylori* was detected in 80% of them.

Conclusion: These results suggest that regular intake of cranberry juice or La1 may be useful in the management of asymptomatic children colonized by *H. pylori*; however, no synergistic inhibitory effects on *H. pylori* colonization were observed when both foodstuffs were simultaneously consumed.

Keywords: *Helicobacter pylori*; *Lactobacillus johnsonii* La1; Probiotics; Cranberry juice; Children; Functional foods

Introduction

Helicobacter pylori is a human pathogen that colonizes the stomach of individuals mostly living in bad hygienic conditions [1]. In Chile, a 10-y epidemiologic survey indicated that approximately 35% of children 4 y of age and 60% of adolescents from a low socioeconomic stratum are colonized by *H. pylori* [2]. This agent is considered an etiologic factor for peptic ulcer and a risk factor for the development of gastric cancer, a highly prevalent pathology in Chile [1,3]. The high prevalence of *H. pylori* in the population, the variable efficiency of the treatment and its high cost, and the fact that asymptomatic people may not be

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treated with antibiotics make important the search for alternative solutions capable of interfering with *H. pylori* in at-risk populations [4,5].

Probiotics have been recently suggested as a new tool in the management of *H. pylori* colonization. It has been proposed that they could act through the production of organic acids and/or bacteriocins capable of inhibiting *H. pylori* growth and its attachment to gastric epithelial cells [5]. *Lactobacillus johnsonii* La1 (La1) is a well-described probiotic strain that has been shown to survive in the gastrointestinal tract of humans and to modulate their colonic microbiota [6]. La1 also stimulates the local and systemic immune systems [7,8] and various studies have indicated that it may also exert antibacterial activities against gastrointestinal pathogens [9,10] including *H. pylori* [11]. These *in vitro* results have been confirmed in clinical trials showing that the administration of some probiotic strains may interfere with *H. pylori* colonization and inflammation and/or decrease the adverse effects associated with the eradication treatment [5,12].

In contrast, extracts of berries such as cranberries, blueberries, and black currants have been shown to exert similar inhibitory activities against *H. pylori*, probably due to their high content of proanthocyanidins [13–15]. In a clinical trial carried out in colonized Chinese adults, cranberry juice was shown to eradicate *H. pylori* in 14.4% of subjects [16]. Because probiotics and cranberry juice inhibit *H. pylori* through different mechanisms, we proposed that a daily intake of both foodstuffs would result in an additive or synergistic effect against this pathogen.

Materials and methods

Subjects

The study was carried out in three schools from medium to low socioeconomic districts in Santiago, Chile, between August and October 2006. Male and female asymptomatic children, 6 to 16 y of age, with a positive ^{13}C-urea breath test (UBT) result and without antecedents of gastrointestinal pathologies, chronic diseases, or a recent history of antibiotic, antacid, or prokinetic drug treatment were recruited. Parents received detailed information about the aims and methodologies of the study, and a written consent form was signed by those who accepted the participation of their children. The protocol was approved by ethics committee of the Institute of Nutrition and Food Technology, University of Chile.

Study design

This was a random, double-blind, controlled study. The first UBT (basal) was carried out in 493 children responding to the inclusion criteria to select those colonized by *H. pylori*. Enrollment and allocation of the children into the experimental groups were carried out by the pediatrician. A table of random numbers generated by computer was used to allocate colonized children into four groups to receive one of the following dietary treatments: cranberry juice and La1 (CB/La1), placebo juice and La1 (La1), cranberry juice and heat-killed La1 (CB), or placebo juice and heat-killed La1 (control). Products were administered to the children in the school every morning for 3 wk under the supervision of a dietician and a pediatrician to ensure compliance with the study protocol. Every child had to ingest 80 mL of a La1-containing product and 200 mL of cranberry juice or the corresponding placebo. Products were not administered during weekends. Parents were asked to avoid giving their children any other commercial probiotic-containing products and cranberry juice throughout the duration of the study. Children who were absent from school for more than 3 consecutive days were discharged. A second UBT was carried out at the end of the 3-wk treatment (time 1) to evaluate the presence or absence of *H. pylori* (primary outcome) and, whenever possible, a third UBT was performed after a 1-mo washout period without treatment in the children who could be contacted (time 2).

Products

The product with the probiotic strain (Chamyto, Nestlé Chile SA, Santiago, Chile) was packaged in 80-mL plastic bottles, providing 11.8 g of carbohydrates, 0.7 g of proteins, and 0.024 g of lipids with a total energy content of 209 kJ. Living La1 was present at concentrations $>10^7$ colony-forming units/mL at the time of ingestion, and fresh batches of product were used weekly to ensure satisfactory La1 intake. The corresponding placebo consisted of the same product but previously heated to 60°C for 15 min and contained only heat-killed La1, as assessed by cultures in de Man-Rogosa-Sharpe agar.

Cranberry juice was prepared daily from cranberry concentrate (Cran Chile, Lanco, Chile) by dilution (4%, v/v) in potable tap water; 0.25 g/L of sucralose was added as a sweetener. The cranberry juice placebo had the same aspect and flavor as the cranberry juice and was prepared with 0.5 g/L of ascorbic acid, 1.8 g/L of citric acid, 0.3 g/L of malic acid, 0.5 g/L of benzoic acid, 0.5g/L of berry flavor, 0.8 g/L of natural coloring, and 0.2 g/L of sucralose. We previously confirmed, by using an agar diffusion assay, that the cranberry juice did not exert any bactericidal activity against *L. johnsonii* La1, thus precluding an inhibitory effect of the juice on the activity of the probiotic in the stomach (data not shown).

^{13}C-urea breath test

To detect *H. pylori* colonization, we used the non-invasive UBT, which is well tolerated by children and has been previously validated in our pediatric population [17,18]. After an overnight fast, children first drank a glass of orange

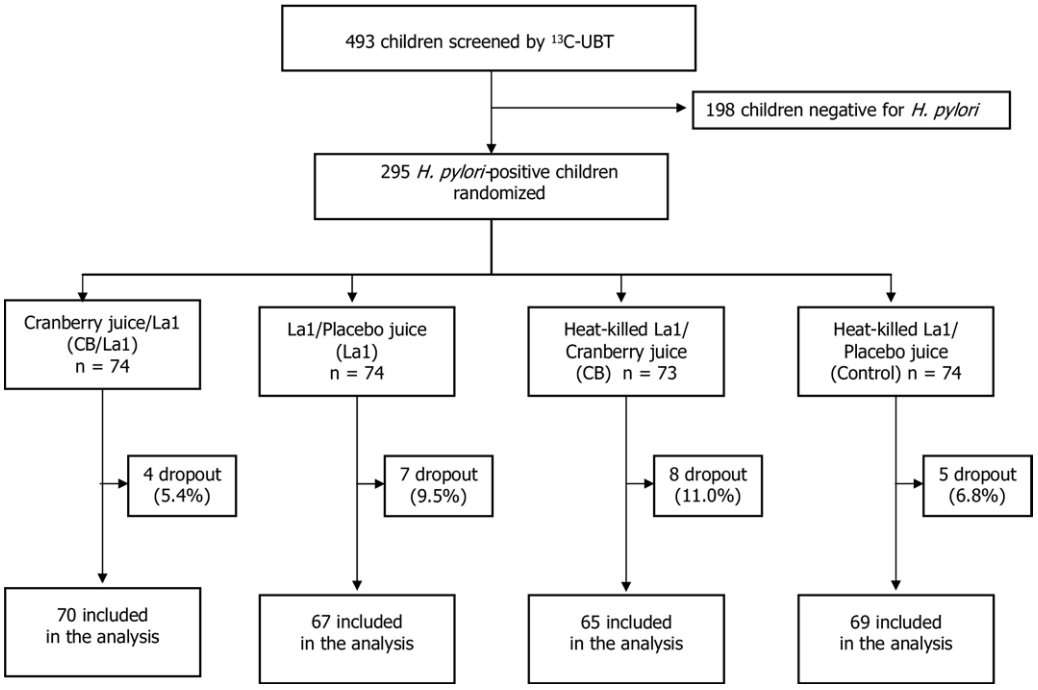

Fig. 1. Flowchart for subject's participation in the study. La1, *Lactobacillus johnsonii* La1; UBT, urea breath test.

juice to delay gastric emptying and then a baseline breath sample was collected in duplicate by blowing with a straw in two glass tubes. Fifty milligrams of ^{13}C-urea in water was then administered to the children and a second breath sample was obtained, also in duplicate, after 30 min. The sample-containing tubes were stored at room temperature until analysis. Breath samples were passed through a desiccant to eliminate water, and carbon dioxide was extracted by gas chromatography at 100°C under vacuum. The ^{13}C/^{12}C ratio in respiratory CO_2 was measured in a stable isotope ratio mass spectrometer (ABCA, Europa Scientific, Cheshire, United Kingdom) equipped with an autosampler and compared with the Pee Dee Belemnite reference limestone standard. Baseline values of $^{13}CO_2$ obtained just before the administration of the labeled urea were subtracted from the 30-min values. The excess $\delta^{13}CO_2$ over baseline (DOB) values were expressed as parts per thousands and a breath test with a DOB >5‰ for the entire 30-min period was considered positive for *H. pylori*. All children received a breakfast after the breath test.

Statistics

Data analysis was done with Statistica 4.5 for Windows (StatSoft, Inc., Tulsa, OK, USA). The primary outcome was the result of the UBT after the 3-wk treatment period. A sample of 69 subjects in each group was calculated assuming an eradication rate of about 20% with the treatments, with $\beta = 0.80$ and $\alpha = 0.05$. Taking into account an approximate dropout rate of 7%, 74 children were included in each experimental group. Eradication rates were compared by chi-square test. DOB values were expressed as mean ± SD. Differences between results of the UBTs carried out at time 1 and at baseline were expressed for each group as the mean of the $DOB_1 - DOB_0$ values with its 95% confidence interval and subsequently compared by analysis of variance.

Results

The basal UBT allowed detection of *H. pylori* in 295 of 493 recruited children (59.8%). The UBT-positive children were enrolled in the study protocol and randomly distributed in the four groups for treatment allocation (Fig. 1). A significant increase in *H. pylori* prevalence was observed with increasing age (6–7 y, 37.5%; 8–9 y, 57.1%; 10–11 y, 54.1%; 12–13 y, 68.9%; and >13 y, 69.9%; $P < 0.001$ by chi-square test). This was higher in the two schools with the lower socioeconomic level (data not shown). Demographic data of the participants and basal DOB values in each group are presented in Table 1; no differences in gender and age or in DOB_0 values were observed between the groups.

Twenty-four children did not complete the study protocol, for a total dropout rate of 8.1%. Twenty-one children were excluded for absenteeism, one for antibiotic treatment, and two because they did not like the products and asked to be withdrawn from the study. No differences in dropout rate were observed between groups.

The eradication rate of *H. pylori* (percentage of negative UBT results) was not significantly affected by age or gender (data not shown). As shown in Figure 2, the eradication

Table 1
Characteristics of the four experimental groups at baseline*

	Control	CB	La1	CB/La1	*P*
No. of subjects	74	73	74	74	
Female (%)	51.3	53.4	43.2	41.9	NS†
Age (y)*	11.8 ± 2.1	11.6 ± 2.3	11.7 ± 2.0	11.4 ± 2.1	NS‡
DOB_0 (‰)*	23.8 ± 14.3	22.1 ± 12.6	21.8 ± 11.1	26.6 ± 13.4	NS‡

CB, cranberry juice; CB/La1, cranberry juice/*Lactobacillus johnsonii* La1; DOB, excess $\delta^{13}CO_2$ over baseline; La1, *Lactobacillus johnsonii* La1
* Mean ± SD.
† Chi-square test.
‡ Analysis of variance.

Table 2
Helicobacter pylori eradication rates in the four experimental groups for different cutoff values for the urea breath test

	Cutoff values			
	<5‰	<4‰	<3‰	<2‰
Control (n = 69)	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)
La1 (n = 67)	10 (14.9%)	9 (13.4%)	7 (10.4%)	6 (9.0%)
CB (n = 65)	11 (16.9%)	9 (13.8%)	8 (12.3%)	6 (9.2%)
CB/La1 (n = 70)	16 (22.9%)	14 (20.0%)	10 (14.3%)	10 (14.3%)
P (chi-square)	0.0028	0.0027	0.018	0.02

CB, cranberry juice; CB/La1, cranberry juice/*Lactobacillus johnsonii* La1; La1, *Lactobacillus johnsonii* La1

rates after the 3-wk period differed significantly among the four treatment groups (P = 0.0028). Suppression was observed in 14.9% (10 of 67) of the children from the La1 group and in 16.9% (11 of 65) of those from the CB group compared with 1.5% (1 of 69) in the control group. In comparison with the La1 and CB groups, the suppression in the CB/La1 group was slightly but not significantly higher (16 of 70, 22.9%).

Because some studies have suggested that the probability of a false-negative result increases (i.e., sensitivity decreases) when the UBT is carried out immediately after treatment [19], the *H. pylori* eradication rates were also evaluated with cutoff values <5‰. As presented in Table 2, the number of negative results decreased with these more restrictive cutoff values but the difference between the groups remained statistically significant.

To evaluate whether treatments decreased the DOB_1 values compared with DOB_0 values, as an indication of a lower intragastric bacterial load [20], mean values of the differences between DOB_1 and DOB_0 (95% confidence intervals) were calculated in the children who remained colonized. No differences were observed between DOB_1 and DOB_0 (control group −2.05‰, −5.25‰ to 1.15‰; CB group −0.76‰, −4.53‰ to 3.00‰; La1 group −0.55‰, −3.53‰ to 2.42‰; CB/La1 group −2.03‰, −5.41‰ to 1.35‰) and between groups (analysis of variance, P = 0.87).

In each group (except the control group, which had only one case of eradication), DOB_0 values were compared to find out whether the subjects who tested negative in the second UBT had lower DOB values at baseline than the subjects who tested positive. No significant differences were observed in the La1 and CB/La1 groups (data not shown), but in the CB group, the DOB_0 values of the children eradicating *H. pylori* were significantly lower than those remaining positive (15.0 ± 7.1‰ versus 23.6 ± 12.4‰, P = 0.037).

The third UBT was carried out in only 19 of the 38 children found to be *H. pylori*–negative in the second UBT: 5, 2, and 12 subjects from the CB, La1, and CB/La1 groups, respectively. Only four children (21%) remained negative after 1 mo without treatment: two from the La1 group and two from the CB/La1 group. Due to the small number of subjects in each group, it was not possible to statistically analyze these results.

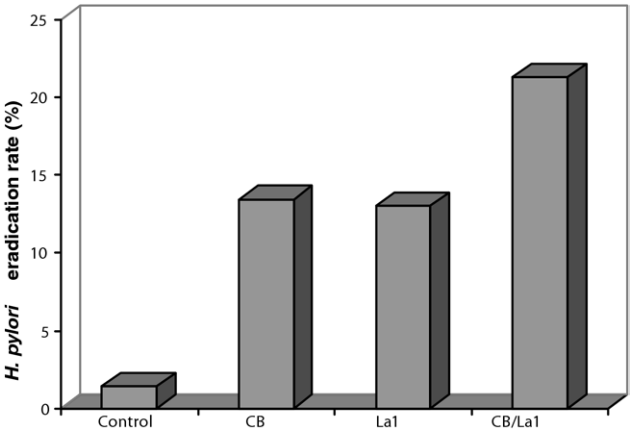

Fig. 2. Eradication rates of *Helicobacter pylori* after 3-wk treatment in children from the control, CB, La1, and CB/La1 groups (chi-square, P < 0.01). CB, cranberry juice/heat-killed *Lactobacillus johnsonii* La1; CB/La1, cranberry juice/living *Lactobacillus johnsonii* La1; control, placebo juice/heat-killed *Lactobacillus johnsonii* La1; La1, placebo juice/living *Lactobacillus johnsonii* La1.

Discussion

This study was carried out to evaluate whether cranberry juice and the probiotic La1 could act additively or synergistically to suppress *H. pylori* in children. Our results show that the proportion of children who tested negative in the second UBT, after the 3-wk period, was significantly higher in the three treated groups compared with the control group. However, no synergistic effects were observed when the cranberry juice and La1 were simultaneously administered; only a partial but not significant additive effect was detected in this group compared with the children receiving cranberry juice or LA1 (+6% and +8%, respectively).

Cranberry (*Vaccinium macrocarpon*) is native to North America where it is widely consumed, its juice being traditionally used for prevention or treatment of urinary tract infections [21]. This property is attributed to the high con-

tent of polyphenols capable of inhibiting the adhesion of uropathogenic bacteria to the urinary tract epithelium [22]. In addition, polyphenols may exert antioxidant and anti-inflammatory activities that may be useful to decrease inflammatory processes, including those associated with pathogen colonization [23,24]. Recent studies have shown that high-molecular-weight compounds (proanthocyanidins) isolated from cranberry extracts can interfere *in vitro* with some adhesins of *H. pylori*, inhibiting its adhesion to the human gastric mucosa [14,15,25]. Furthermore, extracts of different berries and their respective mixtures also exerted bactericidal activities against *H. pylori* strains or increased their susceptibility to clarithromycin [15,26]. These *in vitro* effects have been confirmed in animal models: the administration of cranberry juice for 4 wk resulted in the eradication of the pathogen in 20% of infected mice [27]. Until now, only one study has been carried out in humans: in a randomized, controlled, double-blind clinical trial, Zhang et al. [16] observed that *H. pylori* was eradicated in 14.4% of colonized Chinese adults after 35 d of treatment with 250 mL/d of juice. This result did not change after 90 d of treatment. Our observations confirm those of Zhang et al. and extend them to the pediatric population. A limiting factor for a wider use of cranberry juice is its low acceptability in our population, due to its acidity and astringency. In the future it may be interesting to mix cranberry juice with other fruit juices to increase its tolerance by the populations not familiarized with this product.

Lactobacillus johnsonii La1 is a widely studied probiotic capable of modulating colonic microbiota [6], inhibiting a wide range of pathogens [9,10], and stimulating the immune system in humans [7,8]. It may exert bactericidal activity against *H. pylori* owing to the release of bacteriocin-like compound(s) [11]. Regular intake of a fermented milk containing La1 has also been shown to improve the *H. pylori*–induced gastritis in humans [12]. In a study previously carried out in Chile [17], we observed that a 1-mo treatment with a La1-containing dairy product interfered with *H. pylori* colonization in children, as indicated by the lower DOB values reflecting the decreased urease activity in the stomach [20]. However, we did not observe any case of inhibition, even when La1 was administered with a higher frequency [28]. In consequence, it is striking to observe that in the present study, a 3-wk period of La1 administration resulted in about 15% of children becoming *H. pylori*–negative. It is possible that the characteristics of the infection in our pediatric population have changed during the interval between these two studies due to improvements in sanitation.

The hypothesis that cranberry juice and La1 might act against *H. pylori* in an additive or synergic manner was supported by the fact that the molecules implicated in the inhibition of *H. pylori*, proanthocyanidins and bacteriocins, respectively, differ in their chemical structure and probably also in their mechanisms of action. Synergy against *H. pylori*, for example, has been observed using cranberry and oregano extracts [29]. However, no synergic effects were observed in our study; only a low but non-significant increase of the inhibition of the pathogen was observed when both products were administered simultaneously compared with the effects observed with each product separately.

Similarly to the protocol routinely used to confirm eradication after antibiotic treatment, we carried out a third UBT after a 1-mo washout period in the subjects who had tested negative in the second UBT. Unfortunately, only half of them were available for this third UBT so that the interpretation of these results in relation to the treatments is difficult. However, we observed that nearly 20% of subjects who were *H. pylori*–negative after their treatment remained so after this 1-mo period. These results suggest that in the 80% *H. pylori* had not been really eradicated but only temporary inhibited by the presence of the probiotic or the cranberry juice and that the remaining bacteria were able to recolonize the gastric mucosa once the administration of the inhibiting factors was interrupted. These cases might be considered as false negatives, because it has been shown that carrying out the UBT immediately after treatment decreases its sensitivity, perhaps due to the inhibition of the urease activity from the remaining bacteria [19]. In relation to this finding, it is interesting to note that some polyphenols have also been shown to interfere with *H. pylori* urease activity [30]. In fact, if *H. pylori* is not completely eradicated by the treatment, a low intragastric load may subsist that is not detectable by the UBT. It is considered that, depending on the UBT cutoff value, there is a "gray zone" in which the results of the UBT are inconclusive and should be cautiously interpreted [31]. Using a lower cutoff value, in consequence, may help to maintain the high sensitivity of the UBT after therapy. When a more restrictive cutoff value was used in our study (2‰ instead of 5‰), 16 subjects who were considered negative became positive and thus could be considered falsely negative. However, these changes did not affect our global results and the inhibitory effect of La1 and/or cranberry juice against *H. pylori* colonization remains significant.

The fact that most children negative in the second UBT were positive in the third test may be considered as negative, but it may be seen also under a different light considering that probiotics and cranberry juice are functional foodstuffs that may be regularly consumed by the subjects without risks for prolonged periods.

In conclusion, our study shows that the administration of a product containing La1 or cranberry juice for 3 wk inhibits *H. pylori* in about 15% of asymptomatic, colonized children and that these results may increase slightly when both foodstuffs are consumed simultaneously. In most subjects who became negative, this clearing effect did not persist if these foodstuffs were not consumed. These results confirm that a regular intake of cranberry juice or/and La1 may be useful in colonized asymptomatic pediatric populations.

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