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Research Article

Effect of cranberry juice on eradication of *Helicobacter pylori* in patients treated with antibiotics and a proton pump inhibitor

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Cranberry constituents are known to exert anti-adhesion activity on *H. pylori in vitro.* To determine their possible additive effect to triple therapy with omeprazole, amoxicillin and clarithromycin (OAC), a double-blind randomized clinical study was carried out. One-hundred-seventy-seven patients with *H. pylori* infection treated with OAC for 1 week were randomly allocated to receive 250 mL of either cranberry juice (cranberry-OAC, $n = 89$) or placebo beverage (placebo-OAC, $n = 88$) twice daily and only cranberry juice or placebo beverage for the next 2 weeks. Treatment outcome was determined with the ^{13}C urea breath test (^{13}C-UBT). An additional control group consisted of patients referred to the same center during the same period who were treated with OAC alone for 1 week (non-placebo-OAC, $n = 712$). Overall, the rate of *H. pylori* eradication (^{13}C-UBT < 3.5) was 82.5%, with no statistically significant difference among the three arms. Analysis by gender revealed that for female subjects, the eradication rate was higher in the cranberry-OAC arm ($n = 42$, 95.2%) than in the placebo-OAC arm ($n = 53$, 86.8%) and significantly higher than in the non-placebo-OAC group ($n = 425$, 80%; $p = 0.03$). For males, the rate was nonsignificantly lower in the cranberry-OAC arm (n = 35, 73.9%) than in the placebo-OAC arm ($n = 45$, 80.0%) and non-placebo-OAC group ($n = 287$, 85.0%). These results suggest that the addition of cranberry to triple therapy improves the rate of *H. pylori* eradication in females.

Keywords: Cranberry / Eradication therapy / *Helicobacter pylori*

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1 Introduction

In vitro studies have shown that cranberry juice constituents inhibit the adhesion of a wide range of microbial pathogens, including *Helicobacter pylori* [1–3], uropathogenic *Escherichia coli* [4–9], oral bacteria [10–13], and influenza virus ([14], see also review in this issue). In contrast, adhesion of enterotoxigenic *E. coli* expressing mannose resistant hemagglutinin and of mannose-specific type 1 fimbriated *E. coli* were not affected by the high molecular weight material obtained from cranberry [6]. These anti-adhesion activities were considered responsible for the finding in three randomized controlled trials of a significant beneficial cranberry effect on bacteriuria and urinary tract infections in women [15–17]. Moreover, a mouthwash supplemented with a high molecular weight nondialyzable material (NDM) derived from cranberry reduced the salivary *Streptococcus mutans* count in a randomized controlled population [18]. This effect was attributed to the ability of NDM to inhibit streptococcal adhesion and biofilm formation onto tooth surfaces [18–20].

Based on these findings, together with studies showing that NDM inhibited the adhesion of two-thirds of tested clinical isolates of *H. pylori,* including bacteria expressing sialic acid-specific adhesin [7–9], researchers hypothe-

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Abbreviations: OAC, omeprazol, amoxicillin and clarithromycin; **UBT**, urea breath test

sized that cranberry juice may have the ability to eradicate *H. pylori in vivo*. However, the introduction of cranberry juice p.o. in a mice model of *H. pylori* infection caused a significant clearance of the *H. pylori* mass, but it had no effect on eradicating the pathogen from the gastric lumen [21]. In a randomized controlled study, cranberry juice alone accounted for a 15% of the *H. pylori* eradication, compared to 5% for placebo [22]. Although this effect in naturally infected humans was significant, the rate of eradication was still considerably lower than that of conventional triple therapy. Therefore, using a similar design, we sought to examine the additive effect of cranberry consumption on *H. pylori* eradication in patients receiving treatment with conventional triple therapy.

2 Materials and methods

Since 1998, the *Hp* Central Laboratory of Rabin Medical Center has been performing the ^{13}C-UBT on air samples in all patients with suspected *H. pylori* infection. Briefly, patients are given 75 mg urea labeled with ^{13}C in 200 mL of orange juice. Breath samples are collected before ^{13}C intake (time 0) and 30 min after and analyzed by mass spectrometer (Analytical Precision 2003, UK). The results are expressed as the difference in score between the two time points (delta over baseline). A ^{13}C/^{12}C ratio at T30′-T0′ of 3.5 and above is considered positive for *H. pylori* infection, according to the manufacturer's instructions.

The study population consisted of intent-to-treat patients aged 20 to 74 years tested consecutively for *H. pylori* infection at the laboratory between 1998 and 2003 who were found to have a value of >3.5 on the ^{13}C-UBT. One-hundred-ninety patients were randomized to receive triple therapy with omeprazole, amoxicillin, and clarithromycin (OAC) for 1 week, according to the MACH 1 study [23], with either cranberry juice (cranberry-OAC group) or placebo beverage (placebo-OAC group) and only cranberry juice or placebo beverage for the next 2 weeks. During the 3-week treatment the patients consumed 250 mL of the beverages twice daily, one in the morning and one in the evening. The placebo beverage outwardly resembled the cranberry juice and contained vitamin C, sugar, and natural cranberry flavoring and coloring (to simulate the taste of the cranberry juice). Ocean Spray, Inc. (Middleboro, MA, USA) supplied both the cranberry juice and the placebo beverage. Each patient was given the exact amount of 250 mL beverage boxes needed to complete the study. Patient compliance to the study protocol was assessed by counting the empty cranberry and placebo boxes returned at the repeated ^{13}C-UBT. All laboratory and secretarial procedures were performed double blind.

An additional control group included 712 patients referred to the center at about the same time and had been prescribed triple OAC therapy (non-placebo-OAC group) for 1 week. The patients in this group were described in another study that compared various treatment regimens for *H. pylori* eradication rate [24–25].

At 5 to 7 weeks after completion of the 1-week (non-placebo-OAC group) or 3-week course of therapy (cranberry-OAC and placebo-OAC groups), a second ^{13}C-UBT was performed to evaluate the outcome of treatment. Patients with a second ^{13}C-UBT value of ≥3.5 were categorized as treatment failures, and patients with a value of <3.5 were considered to have undergone successful *H. pylori* eradication. Some of the patients in the successful eradication group were further divided into those with values of <1.7 (*H. pylori* eradication) or 1.7 to 3.5 (partial failure/success of *H. pylori* treatment). All patients signed an informed consent form to participate in the study. The local ethics committee approved the study protocol.

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

2.1 Power calculations

The sample size was calculated to determine a difference in *H. pylori* eradication with cranberry juice consumption. Given an 80% estimated effectiveness of OAC treatment [24], an increase of 10% in *H. pylori* eradication with a one-tailed significance of 0.05 and a power of 90% would require a sample size of 78 patients in each of the cranberry and placebo arms. Anticipating a dropout rate of 10%, we calculated that a total sample size of 170 was needed. For the present study, we recruited 190 patients.

2.2 Statistical analysis

Differences in *H. pylori* eradication among the three main arms were analyzed by Fisher exact test corrected for continuity. The nonparametric Wilcoxon signed ranks test was used to compare differences between the first and the repeated ^{13}C-UBT measurements. All analyses were conducted with SPSS (Statistical Package for the Social Sciences) software (Chicago, IL, version 15).

3 Results

One-hundred-ninety patients were recruited for the placebo-OAC or cranberry-OAC consumption arms. Of these, 13 (6.8%) were excluded because they did not start the study (n = 6) or dropped out of the study during the intervention period [n = 2 (2.2%) from the cranberry group and n = 4 (4.5%) from the placebo group] or did not undergo a second ^{13}C-UBT test (n = 1 from the cranberry group). Thus, the total sample for the analysis consisted of 177

Table 1. Demographic data of patients with a diagnosis of *H. pylori* infection treated with triple therapy with or without cranberry supplement

Characteristic		OAC alone ($n = 712$)	Placebo-OAC ($n = 88$)	Cranberry-OAC ($n = 89$)
Gender	Male	287 (40.3%)	35 (39.8%)	46 (51.7%)
	Female	425 (59.7%)	53 (60.2%)	43 (48.3%)
Mean age ± SD (y)	All	51 ± 14	48 ± 14	45 ± 15
	Male	51 ± 14	49 ± 15	45 ± 17
	Female	52 ± 13	49 ± 14	45 ± 14
Place of birth	Russia/East Europe	162 (22.8%)	17 (19.3%)	19 (21.5%)
	Asia/Africa	166 (23.3%	16 (18.2%)	19 (21.5%)
	Israel	384 (53.9%)	54 (61.4%)	46 (52.3)
	Other	–	1 (1.1%)	5 (5.7%)

Table 2. Eradication rate of *H. pylori* (^{13}C-UBT < 3.5) by gender and type of treatment

Gender	Treatment	No. of patients	*H. pylori* Eradication rate	$p^{a)}$ (Fisher exact test)
Females	Non-placebo-OAC	425	340 (80.0%)	
	Placebo-OAC	53	46 (86.8%)	NS
	Cranberry-OAC	43	41 (95.3%)	0.03
Males	Non-placebo-OAC	287	244 (85.0%)	
	Placebo-OAC	35	28 (80.0%)	NS
	Cranberry-OAC	46	34 (73.9%)	NS
Overall	Non-placebo-OAC	712	584 (82.0%)	
	Placebo-OAC	88	74 (84.1%)	NS
	Cranberry-OAC	89	75 (84.2%)	NS

a) Comparison of rate of eradication between patients treated with OAC and cranberry or placebo with patients treated with OAC only (non-placebo).

patients, of whom 89 were randomized to the cranberry group and 88 to the placebo group. The non-placebo-OAC group included 712 patients diagnosed with *H. pylori* and received the recommended triple OAC therapy for 1 week [23]. The age and gender distributions were similar in the two randomized groups and in the non-placebo-OAC group, which was described elsewhere [24]. Most of the patients in all the groups were native Israelis (Table 1).

Among the 712 OAC patients there were 128 failures (18%) and 584(82%) with successful eradication of *H. pylori* (Table 2). The percent patient with non-ulcer dyspepsia was 43 and 33% (NS) in the failure and eradication groups, respectively. The percent patient with peptic ulcer was 27 and 26% in the failure and eradication groups, respectively (NS). Similar distribution was found in both cranberry-OAC and placebo-OAC group of patients.

The overall rate of *H. pylori* eradication (^{13}C-UBT < 3.5) was 82.5%, consistent with previous findings in the Israeli population [24, 25] (Table 2). There was no significant difference in eradication rate among the groups (82.0, 84.2 and 84.1% in the non-placebo-OAC, cranberry-OAC and placebo-OAC groups, respectively), suggesting that the mere addition of beverage to the triple therapy did not affect the outcome. Thus, the non-placebo group may serve as reference for therapy outcome to which the other arms can be compared.

Further analysis by gender yielded a significant 15% difference in eradication rate between female patients in the cranberry-OAC group (95.2%) and female patients in the non-placebo-OAC group (80.0%) ($p = 0.03$, 95%CI: 3 – 23%) (Table 2). Thus, combined treatment with cranberry juice and OAC was associated with a threefold higher chance for successful eradication in females. Women in the cranberry-OAC arm also had a 8.4% higher *H. pylori* eradication rate than women in the placebo-OAC arm, but this difference did not reach statistical significance ($p = 0.18$). By contrast, for male subjects, the eradication rate for those in the cranberry-OAC arm (73.9%) was lower than that for men in both the non-placebo-OAC group (85.0%) and placebo-OAC arm (80.0%). These differences, however, did not reach statistical significance ($p > 0.1$).

To further examine the effect of cranberry on *H. pylori* eradication, we compared the ^{13}C-UBT values before and after treatment in males and females separately. In this analysis, we included the patients with a second ^{13}C -UBT value of ≥3.5 (treatment failures) and the patients with a second ^{13}C -UBT value between 1.7 and 3.5. A total of 32 subjects had a second test value of > 1.7: 12 females (8 in the placebo-OAC arm and 5 in the cranberry-OAC arm) and 21 males (8 in the placebo-OAC arm and 13 in the cranberry-OAC arm). Consistent with our previous observation in a large number of patients [26], the median ^{13}C-UBT value

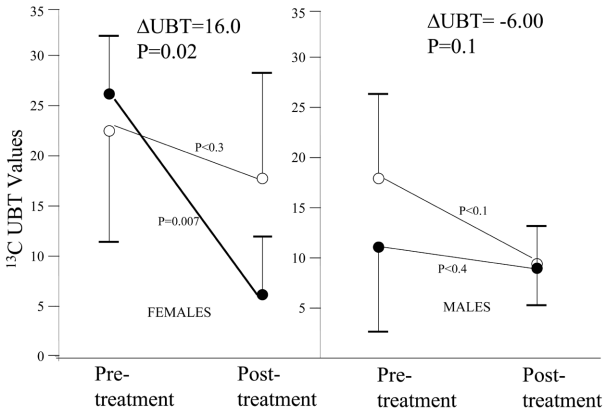

Figure 1. Median ^{13}C-UBT values in patients with treatment failure (^{13}C-UBT ≥ 3.5) or partial failure/success (^{13}C-UBT 1.7–3.5) by type of treatment and gender. The data represent the mean ^{13}C-UBT value (±SD) before and after treatment of 5 females in the cranberry-OAC arm (close circles), 8 females in the placebo-OAC arm (open circles), 8 males in the cranberry-OAC arm (closed circles) and 13 males in the placebo-OAC arm (open circles). Wilcoxon signed ranks test *p* values are shown.

before treatment was significantly higher in females (23.4 ± 10) than in males (13.8 ± 9) ($p = 0.008$, Wilcoxon). Female subjects in the cranberry-OAC arm showed a significant reduction in median ^{13}C-UBT values from before to after treatment (26 ± 10 to 5.9 ± 7; $p = 0.007$, Wilcoxon), whereas males in the cranberry-OAC arm showed only a small and nonsignificant reduction (17.9 ± 9 to 9.4 ± 4, $p = 0.1$) (Fig. 1). In the placebo arm, the reduction in ^{13}C-UBT values was not significant for either gender. Furthermore, the mean reduction in ^{13}C-UBT values after treatment of the 5 females in the cranberry-OAC arm was 20.0 ± 9, which was significantly greater than the mean reduction of 4.1 ± 12 for the 8 females in the placebo-OAC arm ($p = 0.03$). Corresponding values for the male subjects were 1.8 ± 9 (cranberry-OAC) and 8.4 ± 12 (placebo-OAC); this difference was not statistically significant ($p = 0.18$).

4 Discussion

The currently available triple antimicrobial therapy, consisting of proton pump inhibitor and two antibiotics, is effective for the eradication of *H. pylori*. However, there is still no ideal treatment. Significantly, the emergence of strains resistant to one or more of the antibiotics is a major indication for new therapy. Moreover, a significant number of patients (15–20%) respond poorly to primary triple therapy, even when compliance is optimal and the infecting strains are susceptible to the indicated antibiotics [27]. It has been argued that failure of primary triple therapy is more likely in patients with the CYP2C19 wild type because of the altered pharmokinetics of the proton inhibitor [28]. These findings suggest a role of genetic background in treatment failure. Clearly, there is a need to raise the eradication rate from the current rate to a more satisfactory goal of 90–95%. Thus, to be considered effective, any addition to the standard triple therapy regimen would have to diminish the rate of treatment failure by 10–15%.

The purpose of this study was to examine if the addition of cranberry juice, twice daily for 3 weeks, to 1-week triple therapy with OAC can improve the rate of *H. pylori* eradication. OAC therapy alone, in the same medical center and during the same period, was previously found to be associated with an eradication rate of about 80% [24, 25]. Thus, our sample size calculations performed before the trial were aimed to include a sufficient number of patients in the placebo-cranberry arms to show an additional effect of cranberry juice to 90–95% eradication over the control group with a corresponding power (β) of 0.80 and two-sided α of 0.05. When the results clearly showed no statistically significant difference in eradication rate between the placebo and cranberry arms, we further analyzed the results by gender. However, because the gender factor was not considered in the initial design of the study, the size of the placebo-cranberry population was not sufficient to a 10-15% improvement in the cranberry arm. Therefore, we compared the placebo and cranberry arms separately to a group of patients referred to our *Hp Central* Laboratory during the same period and who were treated with OAC alone (non-placebo arm). Researchers have shown that in studies with binary outcomes, the use of non-placebo arms for comparison to the experimental arms was as effective as the use of a placebo arm [29]. The gender analysis clearly showed a 95% rate of eradication for the female patients in the cranberry-OAC group, which was significantly higher than the rate for the female subjects in the non-placebo-OAC group. No such an effect was noted between males in the cranberry-OAC arm and the non-placebo-OAC group.

To gain a better appreciation of the gender-associated effect of cranberry, we reanalyzed the results, with further division of the patients by partial treatment failure/eradication (^{13}C-UBT 1.7–3.5), who represented the upper half of the 0–1.5 range of post-treatment UBT scores. Previous studies have shown that when the levels of ^{13}C-UBT fall below a certain threshold (*i.e.* >3.5), the infection is essentially eradicated [30]. According to our analysis, cranberry juice apparently reduced the *H. pylori* mass below this level of recovery in a significantly higher number of female patients in the study arm compared to the placebo arm. This finding was supported by the significant reduction in the ^{13}C-UBT values of female patients with partial treatment failure/success in the cranberry-OAC arm compared to the placebo-OAC arm (Fig. 1).

The effect of cranberry consumption in human has been so far tested in either females only or in mixed-gender populations. In the former case, there was a beneficial cran-

berry effect in preventing urinary tract infections [15, 16]. In the mixed populations, cranberry consumption significantly increased the eradication of *H. pylori* compared to placebo [22]. Nevertheless, the eradication rate of cranberry alone was far below that of triple therapy.

The present study shows for the first time a gender-associated outcome of triple therapy and supplemental cranberry juice. Our findings also confirm those of previous studies showing no gender-associated outcome of triple therapy alone [24]. Only when cranberry was added to the OAC treatment was a clear gender-associated outcome noted. Evidence implicating gender-associated differences in the biology of *H. pylori* infections is now accumulating. First, increased levels of anti *H. pylori* antibodies were more frequent in females with gastric cancer than in males with gastric cancer and females without gastric cancer [31–33]. Secondly, we noted that the primary UBT values of females before treatment were significantly higher as compared to males [26]. Third, the present study shows that *H. pylori* is eradicated at a significantly higher rate in females prescribed with OAC and cranberry while no such effect was noted in males. Although, taken together, the studies suggest that the biology of *H. pylori* infections in females is somewhat different from that in males; alternative explanations especially to the high eradication rate of *H. pylori* in females prescribed with cranberry-OAC cannot be excluded. Compliance may explain gender-associated differences. Efforts made in the present study to exclude this factor and the fact that there was no gender-difference in triple therapy treatment, makes it unlikely that such gender differences are due to compliance. Sensitivity of the strains to antibiotics, especially clarithromycin, was not tested and may affect the results, although previous studies have shown that virtually all the strains isolated from patients prior to treatment at about the same period were sensitive to clarithromycin [34]. Nevertheless, further studies employing large population are clearly warranted to establish if cranberry affect selectively the eradication rate of *H. pylori* in females.

It is too early to speculate how cranberry in concert with the triple OAC therapy act to increase eradication of *H. pylori* or reduce its mass. The juice lack bactericidal activity [7] but contains anti-adhesion agent (s), which may act to inhibit the adhesion of the bacteria to the gastric mucus and cells and thus renders the planktonic non-adherent bacteria to become more susceptible to the antibiotics as well as to the normal cleansing mechanisms of the gut. This notion is supported by the findings showing that (i) a high molecular weight constituent from cranberry was found to inhibit the adhesion of sialic acid-specific adhesion of *H. pylori* and of two-thirds of clinical isolates of *H. pylori* [1–3]; (ii) ingestion of cranberry alone reduced significantly the rate of eradication in humans and in mice infected with *H. pylori* [21–22]; (iii) *Lactobacillus acidophilus*, a probiotic bacteria, that inhibits adhesion of *H. pylori in vitro* was found to increase significantly the *H. pylori* eradication rate in patients treated with OAC triple therapy as compared to patients treated with OAC alone [35–36] and (iv) killing of adherent *H. pylori* required 100 times more concentrated antibiotics as compared to non-adherent planktonic bacteria [37]. However, if cranberry act in concert with antibiotics and proton pump inhibitor to increase the rate of eradication because it contains anti adhesion agent(s), there is no satisfactory explanation as to why it did so only in females. Our present study with the cranberry perhaps opens a window to explore more gender-associated differences in the complex *H. pylori*-host interactions. If confirmed with large randomized controlled studies, then perhaps a quadruple regiment should be considered for the treatment of *H. pylori* infections consisting of a proton pump inhibitor, two antibiotics and an anti-adhesion agent that act in both males and females.

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5 References

[1] Burger, O., Ofek, I., Tabak, M., Weiss, E. I., *et al.*, A high molecular mass constituent of cranberry juice inhibits helicobacter pylori adhesion to human gastric mucus, *FEMS Immunol. Med. Microbiol.* 2000, *29*, 295–301.

[2] Burger, O., Weiss, E., Sharon, N., Tabak, M., *et al.*, Inhibition of *Helicobacter pylori* adhesion to human gastric mucus by a high-molecular-weight constituent of cranberry juice, *Crit. Rev. Food Sci. Nutr.* 2002, *42(3 Suppl)*, 279–284.

[3] Shmuely, H., Burger, O., Neeman, I., Yahav, J., *et al.*, Susceptibility of *Helicobacter pylori* isolates to the antiadhesion activity of a high-molecular-weight constituent of cranberry, *Diagn. Microbiol. Infect. Dis.* 2004, *50*, 231–235.

[4] Sobota, A. E., Inhibition of bacterial adherence by cranberry juice: potential use for the treatment of urinary tract infections, *J. Urol.* 1984, *131*, 1013–1016.

[5] Zafriri, D., Ofek, I., Adar, R., Pocino, M, Sharon, N., Inhibitory activity of cranberry juice on adherence of type 1 and type P fimbriated *Escherichia coli* to eucaryotic cells, *Antimicrob. Agents Chemother.* 1989, *33*, 92–98.

[6] Ofek, I., Goldhar, J., Zafriri, D., Lis, H., *et al.*, Anti-*Escherichia coli* adhesin activity of cranberry and blueberry juices, *N. Engl. J. Med.* 1991, *324*, 1599–1600.

[7] Ofek, I., Goldhar, J., Sharon, N., Anti-*Escherichia coli* adhesin activity of cranberry and blueberry juices, *Adv. Exp. Med. Biol.* 1996, *408*, 179–183.

[8] Howell, A. B., Cranberry proanthocyanidins and the maintenance of urinary tract health, *Crit. Rev. Food Sci. Nutr.* 2002, *42(3 Suppl)*, 273 – 278.

[9] Howell, A. B., Reed, J. D., Krueger, C. G., Winterbottom, R., *et al.*, A-type cranberry proanthocyanidins and uropathogenic bacterial anti-adhesion activity, *Phytochemistry* 2005, *66*, 2281 – 2291.

[10] Weiss, E. I., Lev-Dor, R., Kashamn, Y., Goldhar, J., *et al.*, Inhibiting interspecies coaggregation of plaque bacteria with a cranberry juice constituent, *J. Am. Dent. Assoc.* 1999, *129*, 1719 – 1723.

[11] Weiss, E. L., Lev-Dor, R., Sharon, N., Ofek, I., Inhibitory effect of a high-molecular-weight constituent of cranberry on adhesion of oral bacteria, *Crit. Rev. Food Sci. Nutr.* 2002, *42(Suppl)*, 285 – 292.

[12] Yamanaka, A., Kimizuka, R., Kato, T., Okuda, K., Inhibitory effects of cranberry juice on attachment of oral streptococci and biofilm formation, *Oral Microbiol. Immunol.* 2004, *19*, 150 – 154.

[13] Labrecque, J., Bodet, C., Chandad, F., Grenier, D., Effects of a high-molecular-weight cranberry fraction on growth, biofilm formation and adherence of *Porphyromonas gingivalis*. *J. Antimicrob. Chemother.* 2006, *58*, 439 – 443.

[14] Weiss, E. I., Houri-Haddad, Y., Greenbaum, E., Hochman, N., *et al.*, Cranberry juice constituents affect influenza virus adhesion and infectivity, *Antiviral Res.* 2005, *66*, 9 – 12.

[15] Avorn, J., Monane, M., Gruwitz, J. H., Glynn, R. J., *et al.*, Reduction of bacteriuria and pyuria after ingestion of cranberry juice, *J. Am. Med. Assoc*. 1994, *271*, 751 – 754.

[16] Kontiokari, T., Nuutinen, M., Sundqvist, K., Pokka, T., *et al.*, Randomised trial of cranberry-lingonberry juice and *Lactobacillus* GG drink for the prevention of urinary tract infections in women, *Brit. Med. J.* 2001, *322*, 1 – 5.

[17] Stothers, L., A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women, *Can. J. Urol*. 2002, *9*, 1558 – 1562.

[18] Weiss, E. I., Kozlovsky, A., Steinberg, D., Lev-Dor, R., *et al.*, A high molecular mass cranberry constituent reduces mutans streptococci level in saliva and inhibits *in vitro* adhesion to hydroxyapatite. *FEMS Microbiol. Lett.* 2004, *232*, 89 – 92.

[19] Steinberg, D., Feldman, M., Ofek, I., Weiss, E. I., Cranberry high molecular weight constituents promote *Streptococcus sobrinus* desorption from artificial biofilm, *Int. J. Antimicrob. Agents* 2005, *25*, 247 – 251.

[20] Steinberg, D., Feldman, M., Ofek, I., Weiss, E. I., Effect of a high-molecular-weight component of cranberry on constituents of dental biofilm, *J. Antimicrob. Chemother.* 2004, *54*, 86 – 89.

[21] Xiao, S. D., Shi, T., N-ethyl-N′-nitro-N-nitrosoguanidine induced gastric carcinoma in wolfdogs – useful animal model for tracing gastric malignancy transformation, *Chinese J. Digestive Dis.* 2003, *4*, 136 – 139.

[22] Zhang, L., Ma, J., Pan, K., Go, V. L., *et al.*, Efficacy of cranberry juice on *Helicobacter pylori* infection: a double-blind, randomized placebo-controlled trial, *Helicobacter* 2005, *10*, 139 – 145.

[23] Lind, T., Veldhuyzen van Zanten, S. J. O., Unge, P., Spiller, R. *et al.*, Eradication of *Helicobacter pylori* using one-week triple therapies combining omeprazole with two antimicrobials: the MACH I Study, *Helicobacter* 1996, *1*, 138 – 144.

[24] Gal, E., Abuksis, G., Fraser, G., Koren, R., *et al.*, 13C-urea breath test to validate eradication of *Helicobacter pylori* in an Israeli population, *Israel Med. Assoc. J.* 2003, *5*, 98 – 100.

[25] Niv, Y., Koren, R., 13C-urea breath test for success of Helicobacter pylori eradication: study of 5885 Israeli patients, *Digestive Dis. Sci.* 2005, *50*, 1513 – 1516.

[26] Shmuely, H., Yahav, J., Samra, Z., Chodick, G., Ofek, I., Elevated C^{13} urea breath test values in women infected with *Helicobacter pylori*, *Dig. Dis. Sci.* 2007, *54*, 402 – 404.

[27] Laheij, R. J., Rossum, L. G., Jansen, J. B., Straatman, H., Verbeek, A. L., Evaluation of treatment regimens to cure *Helicobacter pylori* infection – a meta-analysis, *Aliment. Pharmacol. Ther.* 1999, *13*, 857 – 864.

[28] Schwab, M., Schaeffeler, E., Klotz, U., Treiber, G., CYP2C19 polymorphism is a major predictor of treatment failure in white patients by use of lansoprazole-based quadruple therapy for eradication of *Helicobacter pylori*, *Clin. Pharmacol. Ther*. 2004, *76*, 201 – 209.

[29] Hrobjartsson, A., Gøtzsche, C., Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment, *N. Engl. J. Med.* 2001, *334*, 1594 – 1602.

[30] Suerbaum, S., Michetti, P., *Helicobacter pylori* infection, *N. Engl. J. Med*. 2002, *347*, 1175 – 1186.

[31] Parsonnet, J., Friedmann, G. D., Vandersteen, D. P., Chang, Y. *et al.*, *Helicobacter pylori* infection and risk of gastric carcinoma, *N. Engl. J. Med*. 1991, *325*, 1127 – 1131.

[32] Kikuchi, S., Wada, O., Nakajiama, T., Nishi, T. *et al.*, Serum anti-*Helicobacter pylori* antibody and gastric carcinoma among young adults, *Cancer* 1995, *75*, 2789 – 2793.

[33] Janulaityte-Günther, D., Kupcinskas, L., Pavilonis, A., Valuckas, K., *et al.*, Helicobacter pylori antibodies and gastric cancer: a gender-related difference, *FEMS Immunol. Med. Microbiol.* 2005, *44*, 191 – 195.

[34] Samra, Z., Shmuely, H., Niv, Y., Dinari, G. *et al.*, Resistance of *Helicobacter pylori* isolates in Israel to metronidazole, clarithromycin, tetracycline, amoxicillin, and cefixime, *J. Antimicrobial Chemother.* 2002, *49*, 1023 – 1026.

[35] Canducci, F., Armuzzi, A., Cremonini, F., Cammarota, G., *et al.*, lyophilized and inactivated culture of *Lactobacillus acidophilus* increases *Helicobacter pylori* eradication rates, *Aliment. Pharmacol. Ther.* 2000, *14*, 1625 – 1629.

[36] Sheu, B.-S., Wu, J.-J., Lo, C.-Y., Wu, H.-W., *et al.*, Impact of supplement with *Lactobacillus*- and *Bifidobacterium*-containing yogurt on triple therapy for *Helicobacter pylori* eradication, *Aliment. Pharmacol. Ther*. 2002, *16*, 1669 – 1675.

[37] Megraud, F., Trimoulet, F., Lamouliatte, H., Boyanova, L., Bactericidal effect of amoxicillin on *Helicobacter pylori* in an *in vitro* model using epithelial cells, *Antimiicrob. Agents Chemother.* 1991, *35*, 867 – 872.