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The effect of cranberry supplementation on *Helicobacter pylori* eradication in *H. pylori* positive subjects: a systematic review and meta-analysis of randomised controlled trials

Ronak Nikbazm[1], Zahra Rahimi[2], Yousef Moradi[3], Meysam Alipour[4] and Farzad Shidfar[1]*

[1]*Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran, Iran*
[2]*Department of Epidemiology, School of Public Health, Iran University of Medical Sciences, Tehran, Iran*
[3]*Social Determinants of Health Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran*
[4]*Department of Nutrition, Shoushtar Faculty of Medical Sciences, Shoushtar, Iran*

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Abstract

Helicobacter pylori infection is one of the most common chronic bacterial infections. Cranberry has been suggested for *H. pylori* eradication. We aimed to conduct the first meta-analysis to summarise current evidence on effects of cranberry supplementation on *H. pylori* eradication in *H. pylori* positive subjects. We searched the online databases up to December 2020. Four randomised clinical trials (RCT) were included with human subjects, investigating the effect of cranberry on *H. pylori* eradication. The pooled results were expressed as the OR with 95 % CI. Based on five effect sizes with a total sample size of 1935 individuals, we found that according to the OR, there was a positive effect of cranberry supplementation on *H. pylori* eradication, increasing the chance of *H. pylori* eradication by 1·27 times, but this relationship was not statistically significant (overall OR: 1·27; 95 % CI 0·63, 2·58). The results also indicated the moderate between-study heterogeneity ($I^2 = 63{\cdot}40$ %; $P = 0{\cdot}03$) of the studies. However, there were no significant differences in some subgroup analyses in the duration of treatment, the duration of follow-up and the Jadad score. Our findings revealed that although cranberry had a positive effect on *H. pylori* eradication in adults, this effect was not statistically significant. Due to the small number of included studies and moderate heterogeneities, the potential of cranberry supplementation on *H. pylori* eradication should be validated in large, multicentre and well-designed RCT in the future.

Key words: ***Helicobacter pylori*: Cranberry: Meta-analysis**

Helicobacter pylori is a Gram-negative, spiral-shaped micro-organism which has morphological characteristics penetrate the mucosa and colonise the stomach and duodenum[1,2]. *H. pylori* infection is one of the most common chronic bacterial infections, affecting approximately 4·4 billion individuals worldwide[3]. Reports of infection prevalence rates widely range among geographic regions, reaching the highest levels in developing countries[4]. *H. pylori* infection causes chronic progressive gastric inflammation and a variety of diseases, including gastric and duodenal ulcers and gastric cancer[5]. The WHO has classified *H. pylori* as a group I carcinogen with a risk of stomach cancer[6,7]. Generally, *H. pylori* infection increases the risk of malignancy and the expense of *H. pylori*-associated morbidity[7,8]. Eradication of *H. pylori* infection has been proven to reduce the incidence of gastric cancer[9,10].

Selection of the best drug regimens for eradication of *H. pylori* infection is already challenging[1]. The treatment plan currently adopted as a first-line option includes a combination of a proton pump inhibitor, clarithromycin and amoxicillin or metronidazole/tinidazole, according to international guidelines[11,12]. This therapy persists during 7–14 d, twice a day[11]. Eradication rates of *H. pylori* treated with a 14-d triple therapy reached only 70 % in non-ulcer dyspepsia patients and 80 % in patients with peptic ulcers[11]. The success rate in most European, Asian and North American countries is constantly declining, and low cure rates with 20–45 % have been recently reported[13].

This eradication rate is distant from the desirable rate of infectious diseases and from that proposed by the WHO[12,14]. The main limitation of the current therapy results from the lack of therapeutic compliance, due to the incidence of side effects

Abbreviation: RCT, randomised clinical trial.

* **Corresponding author:** Farzad Shidfar, email shidfar.f@iums.ac.ir

and the discomfort resulting from the multiple doses[15,16]. These factors may lead to the development of antibiotic resistance[16]. Moreover, antimicrobial agents such as amoxicillin and clarithromycin are degraded by gastric acid[14]. Therefore, it is necessary to use higher doses which are reflected in the increase of gastrointestinal side effects, and consequently the discontinuation of the therapy[16]. The bacteria are sensitive to other antimicrobial drugs, nevertheless they cannot be used in the acidic medium[14]. Despite all the endeavours, the current therapy presents many limitations which have led to the failure of *H. pylori* eradication[2]. To overcome these limitations, modification of therapeutic strategies[5] and novel effective therapies have been proposed, including phytomedicine[17]. So far, many compounds found in dietary and medicinal plants, herbs and fruit extracts have been shown to possess antimicrobial activities[18].

Cranberry (*Vaccinium macrocarpon*), belonging to the Ericaceae family, is a fruit widely consumed in many countries[19]. Cranberry contains a number of phytochemicals which have bioactive properties when consumed, including proanthocyanidins, anthocyanin pigments, flavonol glycosides and certain acids[20]. Also, cranberries have been highly ranked in terms of their antioxidant capacity and are known as a rich source of phenolic compounds.

In recent studies, cranberry has been tested both *in vitro* and in clinical trials and promised a non-pharmacological treatment to manage *H. pylori* infections[20]. *In vitro* studies demonstrated that cranberry extract especially containing A-type proanthocyanidins prevented adhesion of *H. pylori* sialic acid-specific strains to human gastric mucus and stomach cells[21]. Also, cranberry has been clinically shown to suppress infections when regularly consumed[21]. Some studies have shown that cranberry juice constituents inhibited the adhesion of a wide range of microbial pathogens, including *H. pylori*, *E. coli* and oral bacteria (1) while others did not find any significant effect[21,22]. Surprisingly, in a double-blind randomised, placebo-controlled trial (RCT) of *H. pylori* positive individuals, there was no statistically significant difference in eradication rates across comparison groups[22].

However, results from human studies have remained inconclusive. Overall, given the presence of conflicting results on the effect of cranberry extract on *H. pylori* eradication, to summarise the evidence and clarify these inconsistencies in the results of human trials, the current systematic review and meta-analysis were conducted to systematically identify and quantitatively assess the efficacy of cranberry supplementation on *H. pylori*-positive individuals.

Methods

Protocol registration

The protocol has been registered on the PROSPERO website as CRD42021232808, available from: https://www.crd.york.ac.UK/prospero/display_record.php?ID = CRD42021232808.

Search strategy

A comprehensive literature search was carried out to identify and appraise investigations which had assessed the effects of cranberry supplementation on *H. pylori* eradication. Electronic databases, including Pubmed (http://www.ncbi.nlm.nih.gov/pubmed), Scopus (http://www.scopus.com), Cochrane Library (http://www.cochranelibrary.com), Web of Knowledge (http://www.webofscience.com) and Google Scholar (http://scholar.google.com) were browsed up to 26 December 2020.

The following keywords in any possible combination were used in the Pubmed search strategy: ((Cranberry (tiab) OR Vaccinium macrocarpon (tiab) OR Viburnum (tiab) OR Cranberry supplementation (tiab) OR Vaccinium (tiab) OR Vaccinium oxycoccus (tiab) OR Vaccinium erythrocarpum (tiab) OR Cranberry juice (tiab) OR Cranberry extract) AND (*Helicobacter pylori* (tiab) OR *H. pylori* (tiab) OR *Helicobacter pylori* Eradication (tiab) OR *H. pylori* Eradication)).

The following keywords were used in the Scopus search strategy: ((TITLE-ABS-KEY Cranberry TITLE-ABS-KEY OR Vaccinium macrocarpon TITLE-ABS-KEY OR Viburnum TITLE-ABS-KEY OR Cranberry supplementation TITLE-ABS-KEY OR Vaccinium TITLE-ABS-KEY OR Vaccinium oxycoccus TITLE-ABS-KEY OR Vaccinium erythrocarpum TITLE-ABS-KEY OR Cranberry juice TITLE-ABS-KEY OR Cranberry extract) AND (*Helicobacter pylori* TITLE-ABS-KEY OR *H. pylori* TITLE-ABS-KEY OR *Helicobacter pylori* Eradication TITLE-ABS-KEY OR *H. pylori* Eradication)).

The search was independently carried out by two authors (RN and ZR), and the obtained articles were assessed. Also for screening, they assessed the articles through the review of titles and abstracts; and if necessary, full texts. After screening, the full texts of remained articles were evaluated based on inclusion criteria to identify the studies eligible for this systematic review and meta-analysis. At each stage, doubtful cases were discussed within the research team.

The references from selected articles and reviews were manually searched to identify references which may have been missed in our primary search and additional studies. No language, population or publication year restrictions were enforced. All searched studies were included in the Endnote software for screening.

Trial registers have been searched using Current Controlled Trials (http://www.controlled-trials.com/), Clinical-Trials.gov (http://clinicalTrials.gov/ct2/home) and the WHO International Trials Registry Platform search portal (http://www.who.int/trialsearch/ Default.aspx). Iranian Registry of Clinical Trials (https://www.irct.ir/) and the Grey literature have been searched using Open Grey (http://www.opengrey.eu).

Study selection

The following pre-specified inclusion criteria were used:

(1) parallel or crossover RCT; (2) RCT with patients were defined as infected by *H. pylori* if they tested positive by any of the following tests: the histology, culture, serology, stool antigen, urea breath test or rapid urease test; (3) comparison of the intervention group consumed cranberry juice/extract/powder *v.* placebo or non-placebo control for suppression of *H. pylori*; (4) RCT with at least 1 week duration of intervention; (5) RCT which reported *H. pylori* eradication or suppression as the outcome and clinical trials with an additional intervention

group were considered as two separate studies and (6) enrolled adult participants (aged > 18 years).

The following was defined as exclusion criteria:

(1) duplicated data; (2) those with a cohort, cross-sectional and case–control design, review articles and ecological studies.

Screening and final selection of articles were performed based on the inclusion and exclusion criteria by two authors (RN and ZR) separately and independently. In the event of a dispute, the views of the third author (YM) were applied to resolve it.

Data extraction

Two independent investigators (RN and ZR) performed data extraction from each eligible RCT. The following information was extracted:

(1) the first author's last name; (2) the year of publication; (3) the study location (the country); (4) the study design; (5) individuals' characteristics (the mean age and sex); (6) the sample size (control and intervention groups); (7) the type of cranberry prescribed; (8) the dosage of cranberry; (9) the duration of intervention; (10) the type of intervention in comparison groups; (11) participant health conditions; (12) the outcome assessment method throughout the trial for the intervention and control groups and (13) the main outcome.

Quality assessment checklists

The Cochrane Risk of Bias Tool for Randomised Controlled Trials[23] was used by two separate authors (RN and ZR) to explore potential risks of bias. These scales include items to assess the adequacy of random sequence generation, allocation concealment, blinding as well as the detection of incomplete outcome data, selective outcome reporting and other potential sources of bias. Based on the recommendations of the Cochrane Handbook, judgement of each item was recorded as the 'Low', 'High' or 'Unclear' risk of bias.

A 'high risk' score was given to each domain if the study comprised methodological defects which may have affected its findings, a 'low risk' score if there was no defect for that domain and an 'unclear risk' score if the information was not sufficient to determine the impact (Fig. 2).

Any disagreement in the data extraction and the risk of bias assessment was settled by a third researcher (YM).

Also, this study was performed in accordance with the Jadad score checklist for the Quality Assessment Checklist for Individual Studies for Systematic Reviews and Meta-Analyses and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses instructions[23].

Statistical analysis

The ultimate goal of this study was to determine whether the cranberry group had a higher *H. pylori* eradication rate than the placebo group. OR were used to measure the effect of cranberry supplementation on *H. pylori* eradication rates using the random effects model. Heterogeneity in meta-analysis may be defined as 'the variability between studies in the estimates of effects' and can be categorised as statistical heterogeneity, methodological heterogeneity and clinical heterogeneity. The potential sources of clinical heterogeneity include different study participants, different interventions and different outcome measures across individual studies. Statistical heterogeneity was analysed with χ^2 distribution, Cochran's Q-test and I^2 statistics. Inter-study heterogeneity was quantitatively explored using Cochran's Q and I^2 statistics. In this regard, I^2 values of 50 and 75 % indicated substantial and considerable heterogeneity, respectively[24]. The I^2 statistic was under 50 % and/or the Q-test was not significant at $P < 0{\cdot}05$.

Based on the detected heterogeneity between studies, a random effects or fixed model was applied in the meta-analysis[24,25]. To obtain the overall effect sizes, we applied a random effects model which took between-studies variations into account. Effect sizes were presented as the OR with 95 % CI, and P-values < 0·05 were considered statistically significant.

In order to assess potential sources of heterogeneity in the meta-analysis, the association between the treatment effect and other study characteristics is often used to methods such as meta-regression and subgroup analysis, including the duration of the intervention (≥ 50 *v.* < 50 d) and (≥ 100 *v.* < 100 d) and the Jadad score. We drew a funnel plot to evaluate the publication bias.

Sensitivity analysis was used to detect the dependency of the overall effect size on a particular study. In addition, the Egger test was used to assess publication bias. All analyses were carried out through the application of the metan and metabias commands in Stata 16.0 (Stata Corporation).

Double data checking

For more assurance on the quality of results, the PI of the study rechecked the full-text data and the analysed data.

Results

Study characteristics

A total of 1461 articles were recruited through the searches, the titles and abstracts of which were assessed by two independent reviewers. Finally, four articles were remained for analysis (Fig. 1).

These RCT were published between 2005 and 2020. Four studies were performed on both sexes. The sample size of included RCT varied from 134 to 889 participants. A total sample size was 1935 individuals. Studies were conducted in China[21,22], Iran[1] and Israel[26]. The mean age of participants was between 11 and 50 years. The dosage of cranberry varied from 200 to 560 ml/d, and the duration of intervention ranged from 14 to 90 d across selected RCT.

All studies applied a parallel design, one of them was a multicentre study[22] and one trial was a dose–response study[21]. The type of cranberry intake in three trials was the juice form[21,22,26], two trials administered the capsulated form[1] and one trial performed the intervention with both[21]. RCT were performed on healthy individuals[21,22,26] and patients with the peptic ulcer disease[1]. The characteristics of four RCT included in the current systematic review and meta-analysis are shown in Table 1.

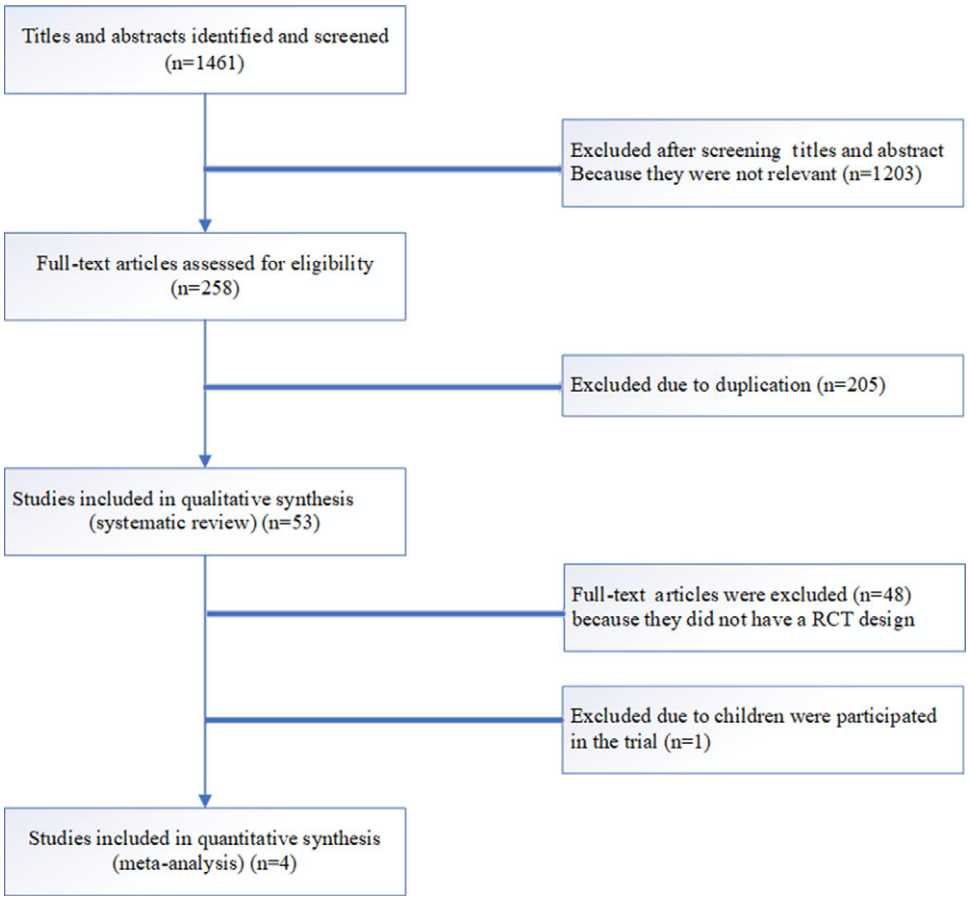

Fig. 1. Flow diagram of excluded and included studies in this meta-analysis.

Assessing for risk of bias

Except for the research of Li *et al.*[21], none of the included studies reported adequate information for the methods used for performing random sequence generation.

Only Shmuely *et al.*[22] reported adequate information for the methods used for performing allocation concealment. Also, the study of Seyyedmajidi *et al.*[1] and included RCT had double-blind designs.

The reasons for dropouts were addressed by all studies[1,21,22,26].

The studies of Li *et al.*[21] and Zhang *et al.*[26] reported adequate information for the selective reporting[1,22]. Details on the judged risk of each item of bias among the included trials are presented in Figs. 2, 3 and Table 2.

Findings from the systematic review

Among four studies assessing the *H. pylori* eradication, two studies overall revealed a significant effect of cranberry on *H. pylori* eradication rate[1,26], whereas one study reported a significant effect of cranberry on *H. pylori* eradication rate in the female but did not reach statistical significance in the men[22]. Also, one trial revealed a significant effect in the intervention group consumed cranberry juice but those which administrated encapsulated cranberry powder doses did not show any significant effect. In total, four RCT with a total sample size of 1934 subjects were included in the analysis[1,21,22,26].

Findings from the meta-analysis

The study results are shown in a forest plot in Fig. 4. The results indicated that the pooled OR was (OR: 1·27; 95 % CI 0·63, 2·58; $I^2 = 63{\cdot}40\,\%$; $P = 0{\cdot}03$). Although cranberry supplementation intake had a risk effect on *H. pylori* eradication, however, this effect was not statistically significant (Fig. 4). One study was discarded for the following reason: children were participated in the trial unlike other studies. But five effect sizes were obtained from the included studies. The results also indicated the moderate between-study heterogeneity ($I^2 = 63{\cdot}40\,\%$; $P = 0{\cdot}03$) of the studies.

Subgroup analysis

In order to detect potential sources of heterogeneity in the meta-analysis, subgroup analyses were performed. Table 3 shows subgroup analysis based on the duration of treatment, the duration of follow-up and the Jadad score by cranberry supplementation intake and *H. pylori* eradication.

The OR for the duration of treatment < 50 and ≥ 50 d were (OR: 1·71; 95 % CI 0·62, 4·70; $I^2 = 69{\cdot}56\,\%$; $P = 0{\cdot}07$) (Fig. 5) and (OR: 0·99; 95 % CI 0·34, 2·91; $I^2 = 65{\cdot}30\,\%$; $P = 0{\cdot}05$),

British Journal of Nutrition

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Table 1. Characteristics of included studies

First author	Year	Country	Clinical trial design/ randomised/blinding	Treatment group	Control group	Sex	Age mean	Health condition	Dose/day	Duration of treatment (day)	Follow-up day	Outcome assessment method	Bacteria detection
Seyyed Majidi *et al.*[1]	2016	Iran	RCT (parallel/randomised, controlled, open-label)	100	100	Female and male	50·29 ± 17·79 years	*H. pylori*-positive with the peptic ulcer disease	500 mg capsule	14	56	*H. pylori* eradication rate (%)	^{13}C-urea breath test (89 %)
Li *et al.*[21]	2021	China	RCT (parallel/randomised, controlled, double-blind/ dose–response)	(*n* 76) Medium (cranberry encapsulated powder (36 dose/d (mg))) (*n* 76) High (cranberry encapsulated powder(72 dose/d (mg)))	76	Female and male	47·24 ± 11·53 years	*H. pylori*-positive	560 mg capsulated powder	56	101	*H. pylori* eradication rate (%)	^{13}C-urea breath test (92·1 %)
Li. *et al.*[21]	2020	China	RCT (parallel/randomised, controlled, double-blind/ dose–response)	(*n* 73) Medium (cranberry juice (44 dose/d (mg))) (*n* 74) High (cranberry juice (88 dose/d (mg)))	77	Female and male	47·24 ± 11·53 years	*H. pylori*-positive	480 mg juice	56	101	*H. pylori* eradication rate (%)	^{13}C-urea breath test (82·4 %)
Shmuely *et al.*[22]	2007	Israel	RCT (parallel/randomised, controlled, double-blind)	89	88	Female and male	Treatment (45 ± 1), control (48 ± 1)	*H. pylori*-positive	500 ml juice	21	77	*H. pylori* eradication rate (%)	^{13}C-urea breath test (84·2 %)
Zhang *et al.*[27]	2005	China	RCT (parallel/randomised, controlled, double-blind)	97	92	Female and male	48·9 ± 11·2	*H. pylori*-positive	500 ml juice	90	181	*H. pylori* eradication rate (%)	^{13}C-urea breath test (14·4 %)

(Fig. 6) respectively (Table 3). Also, the OR for the duration of follow-up < 100 and ≥ 100 d were (OR: 1·71; 95 % CI 0·62, 4·70; $I^2 = 69{\cdot}56$ %; $P = 0{\cdot}07$) and (OR: 0·99; 95 % CI 0·34, 2·91; $I^2 = 65{\cdot}30$ %; $P = 0{\cdot}05$), respectively (Table 3). However, the OR for the Jadad score (3) and the Jadad score (7) were (OR: 1·02; 95 % CI 0·13, 8·13; $I^2 = 90{\cdot}02$ %; $P = 0{\cdot}00$) and (OR: 1·72; 95 % CI 0·78, 3·78; $I^2 = 0{\cdot}00$ %; $P = 0{\cdot}8$), respectively (Fig. 7) (Table 3). Due to the low number of studies which reported the Jadad score[5], subgroup analysis was performed but not applicable. Also due to the low number of studies, subgroup analysis was not applicable to other variables.

Meta-regression

The meta-regression analysis was conducted to evaluate whether the changes in outcomes in response to cranberry supplementation could be associated with the duration of follow-up. The results indicated that *H. pylori* eradication was not significantly associated with the duration of treatment by cranberry intervention (coefficient = 0·009; *P*-value = 0·8; SE = 0·053; 95 % CI −0·09, 0·11).

Assessment of publication bias

To evaluate publication bias related to the meta-analysis, we can use the metabias function from the Stata and a funnel plot. The results of publication bias are shown in Fig. 8. We saw that the number of studies at the left and the right sides of the funnel plot was almost the same, indicating no detected publication bias. Also, when we did the Egger's regression tests ($P = 0{\cdot}57$; SE = 4·94; $B = -2{\cdot}8$), no significant publication bias was seen. Using the 'trim and fill' method, any significant result was not observed (0·24, 95 % CI −0·466, 0·947) for this meta-analysis.

Sensitivity analysis

Sensitivity analysis showed that the overall effect size regarding the effects of cranberry supplementation on *H. pylori* eradication did not depend on a single study 1·27 (CI range: 0·63, 2·58). All studies have included this amount. However, in some studies, such as the second, third and fourth studies, the maximum CI has been greater than the overall CI. In the other word, elimination of each RCT at one time or simultaneous elimination of fair and low quality RCT (studies with high risks of bias) did not significantly change the overall estimates of cranberry supplementation on *H. pylori* eradication (Fig. 9).

Figure 10 shows the L'Abbé plot for the eradication rate of *H. pylori* in both the treatment and the control groups. Each circle represents an individual trial and the larger circles represent trials with more participants. The solid diagonal line indicates that the *H. pylori* eradication rate is equal in the two arms within trials. The dotted line may be called 'the overall OR line', as it represents a rate ratio estimated by pooling the results of all studies. The graph shows that the effect size (the OR) of the majority of studies included in the present meta-analysis (four studies) is above 1 and shows the significant effect of supplementation for the eradication of *H. pylori*.

Table 2. The summary of review authors' judgements on each risk of bias item for included studies based on the Cochrane risk of bias checklist (95 % confidence intervals)

Name	Random sequence generation	Allocation concealment	Blinding of outcome assessment	Incomplete outcome data (attrition bias)	Selective reporting	Effect size	95 % CI
Seyyedmajidi *et al.* (2016)	Unclear	Unclear	Unclear	L	U	2·84	1·32, 6·14
Li *et al.* (2020)	Low	Unclear	Low	L	L	1·91	0·61, 5·98
						1·57	0·53, 4·64
Shmuely *et al.* (2007)	Unclear	Low	Low	L	U	1·01	0·45, 2·27
Zhang *et al.* (2005)	Unclear	Unclear	Low	L	L	0·34	0·12, 0·99

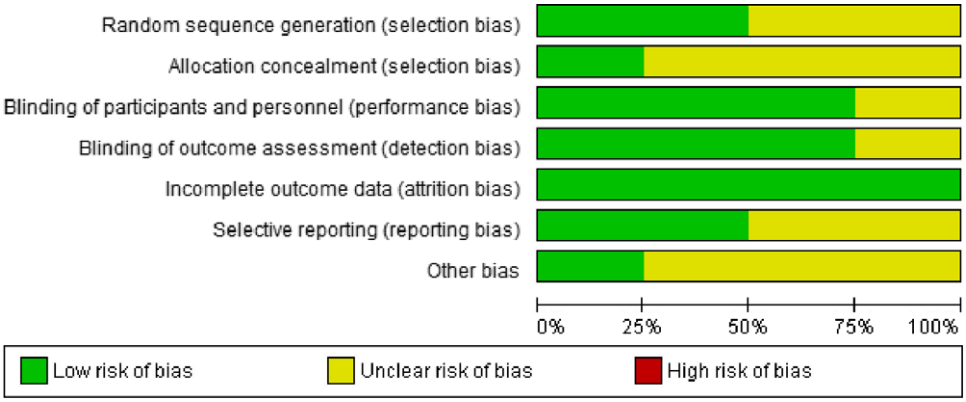

Fig. 2. Risk of bias summary.

Table 3. Subgroup analysis based on the duration of treatment, the duration of follow-up and the Jadad score (Odds ratios and 95 % confidence intervals)

Subgroup	Number of studies	Sample size	Summary		Between studies		Q
			OR	95 % CI	I^2	*P* heterogeneity	
Duration of treatment							
< 50 d	2	377	1·71	0·62, 4·70	69·56 %	0·07	3·28
≥ 50 d	3	492	0·99	0·34, 2·91	65·30 %	0·05	5·81
Duration of follow-up							
< 100 d	2	377	1·71	0·62, 4·70	69·56 %	0·07	3·28
≥ 100 d	3	492	0·99	0·34, 2·91	65·30 %	0·05	5·81
Jadad score							
Score (3)	2	389	1·02	0·13, 8·13	90·02 %	0·00	10·02
Score (7)	2	303	1·72	0·78, 8·78	0·00 %	0·8	0·06

Discussion

Our systematic review and meta-analysis indicated that although cranberry supplementation intake had a risk effect on *H. pylori* eradication, however, this effect was not statistically significant.

There is a controversy on the cranberry effect on the outcomes of *H. pylori* eradication. Despite the present and another study[22] did not confirm a significant effect of cranberry on *H. pylori* eradication, some studies have suggested that people who regularly consumed cranberry had significantly *H. pylori* suppression than others[1,27]. For example, a study conducted on the effect of cranberry on *H. pylori* eradication with a standard therapy including lansoprazole, clarithromycin and amoxicillin in patients with the peptic ulcer disease revealed that the addition of cranberry to lansoprazole, clarithromycin and amoxicillin triple therapy for *H. pylori* has a higher rate of eradication than the standard regimen alone[1].

Some findings demonstrated the effect of cranberry consumption on *H. pylori* eradication in demographic subgroups[28] or a specific form of cranberry. So that, animal[29,30,34] and human studies have shown that the consumption of cranberry juice can be effective in eradicating *H. pylori*[26,28]. On the other hand, some studies suggested that

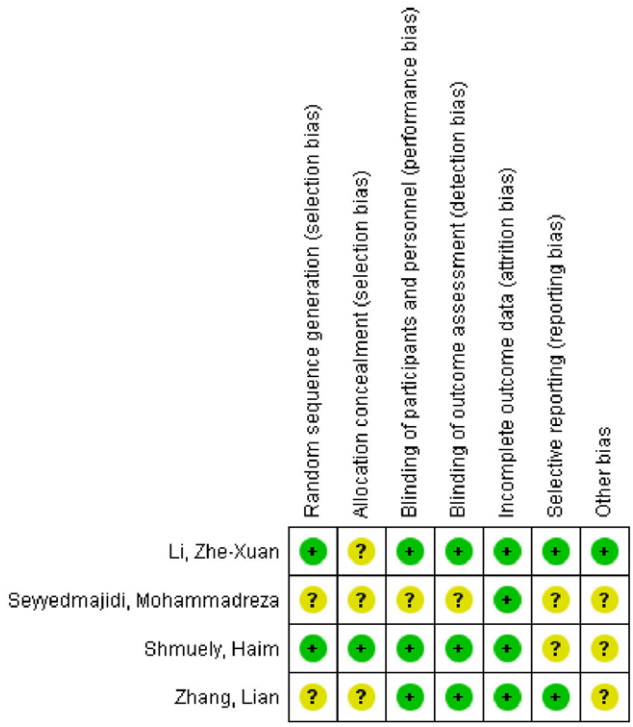

Fig. 3. Risk of bias summary.

cranberry had anti-*H. pylori* properties in *in vitro*, animal and clinical models which indicated that cranberry consumption alone or administered with antibiotics could reduce *H. pylori* colonisation but might not fully eradicate it[25]. This properties of cranberry could be due to a high molecular mass constituent derived from cranberry juice inhibited the sialic acid-specific adhesion of *H. pylori* to human gastric mucus and to human erythrocytes. Also, present proanthocyanidin[20], vitamin C and bioflavonoids with antioxidant properties and a high molecular weight constituent of cranberry juice which may also contribute to the bacteriostatic effect of its juice. The recent study revealed that cranberry juice could inhibit *H. pylori* adhesion to the human gastric mucosa *in vitro*. These results were not obtained in powder form[25,28].

We found that inconsistent in the results of studies may be due to differences in study designs, study populations or sample sizes, intervention durations, follow-up durations and/or different doses of cranberry. In most of the studies, juice and dried fruit of cranberry were used and maybe the capsule forms are not as effective as the other forms[1].

Strengths and limitations

To the best of the authors' knowledge, the present systematic review and meta-analysis is the first study that evaluates the evidence of cranberry effectiveness on *H. pylori*. However, the current meta-analysis has some limitations which should be considered. The number of included RCT was low, especially in subgroup analysis.

First, potential publication bias may exist in the observed results since only some established electronic literature databases were searched. Second, due to the lack of detailed information, the quality assessment of the eligible studies may have been influenced by personal judgements.

Third, the heterogeneity of the overall results was moderate in terms of the duration of intervention and the Jadad score, which may have not significantly affected the efficacy of the results. Finally, the results of subgroup analysis in the present meta-analysis based on the duration of treatment, the duration of follow-up and the Jadad score showed that the amount of heterogeneity did not significantly decrease compared with those of the overall analysis. Therefore, these factors (the duration of treatment, the duration of follow-up and the Jadad score) cannot play a significant role as factors in creating heterogeneity between studies. It is possible that other factors, such as how the outcome is measured or important factors not mentioned in the selected initial studies, may play a major role in heterogeneity. It should not be overlooked that the number of studies included in the meta-analysis was small, which can also have a significant impact on not finding sources of heterogeneity.

Conclusion

In conclusion, the results of this systematic review and meta-analysis showed that although there was a positive effect of

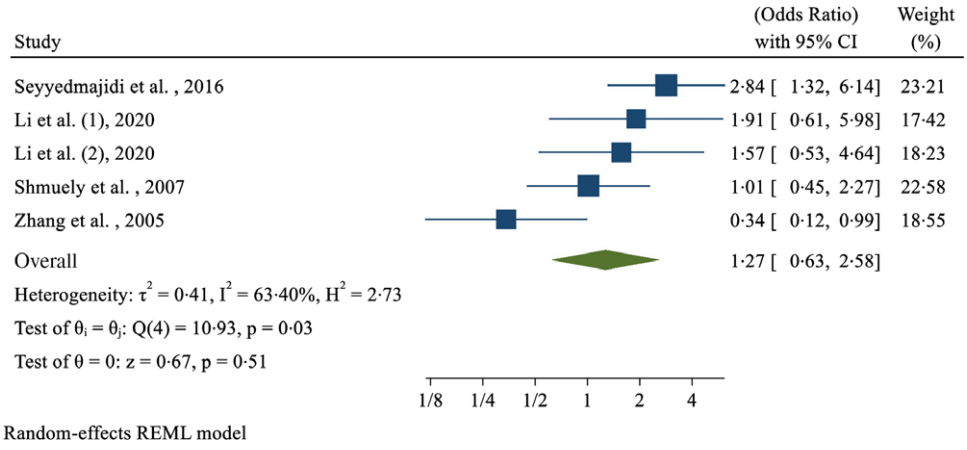

Fig. 4. The meta-analysis results of the effect of cranberry supplementation on Helicobacter pylori.

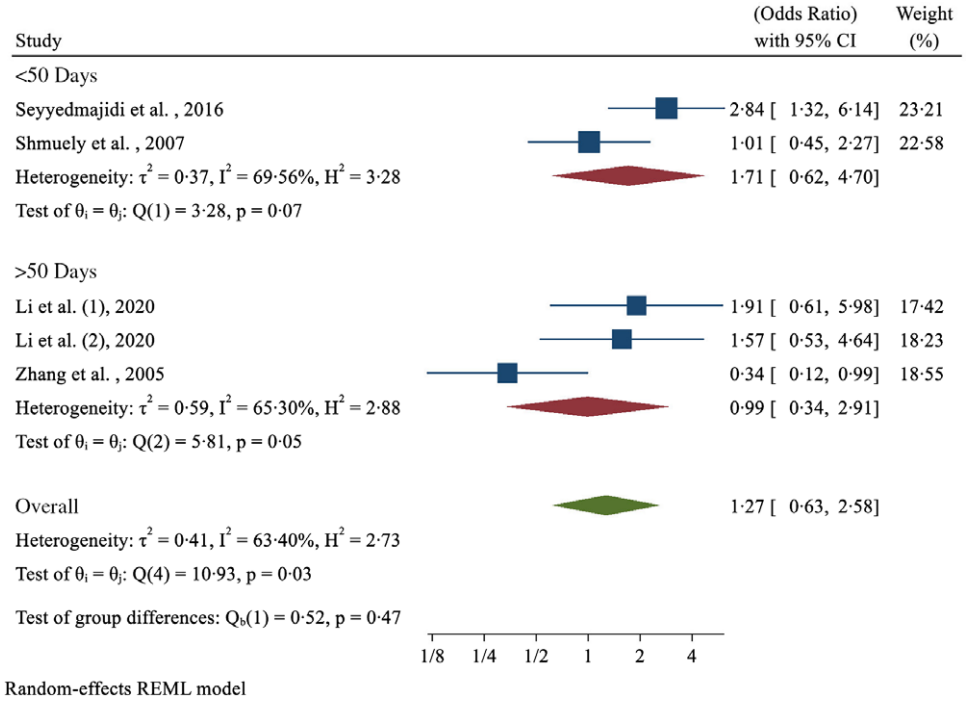

Fig. 5. The meta-analysis results of the effect of cranberry supplementation on duration of treatment (<50 days and >50 days).

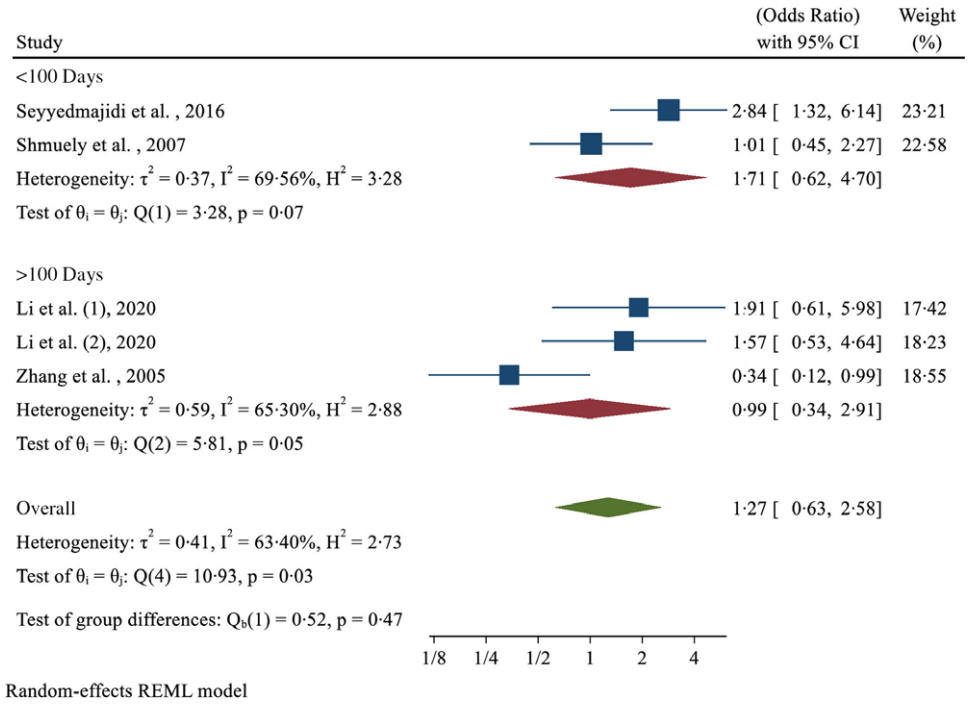

Fig. 6. The meta-analysis results of the effect of cranberry supplementation on duration of follow up (<100 days and >100 days).

cranberry supplementation on *H. pylori* eradication, and it increased the chance of *H. pylori* eradication by 1·27 times, this relationship was not statistically significant. However, based on the moderate heterogeneity among the included studies, further investigation is needed to evaluate the best dosage, form, duration of follow-up and the optimum effect of cranberry on *H. pylori* eradication. In the future, more RCT with more subjects and higher quality are still needed.

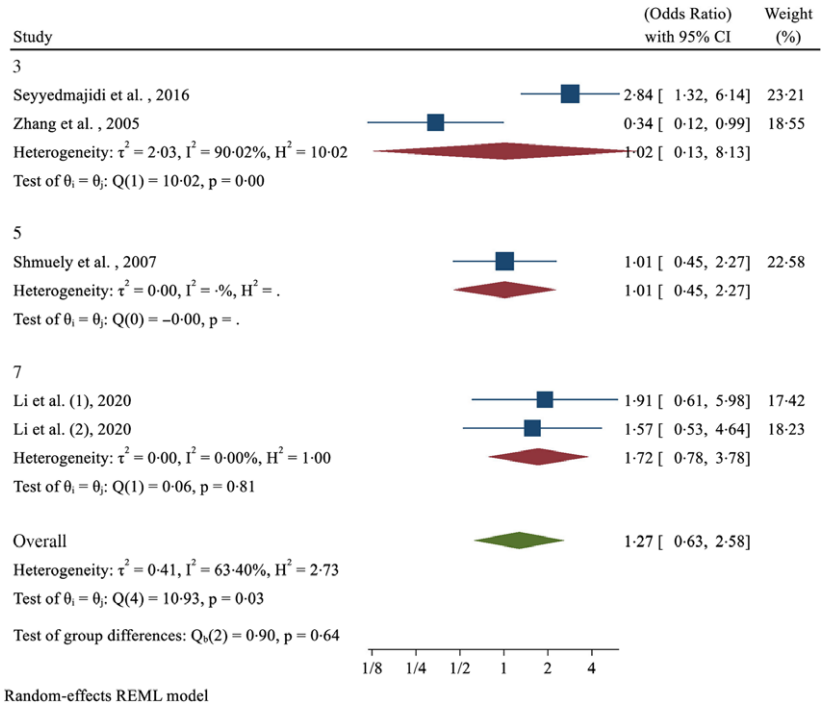

Fig. 7. The meta-analysis results of the effect of cranberry supplementation on Jadad score.

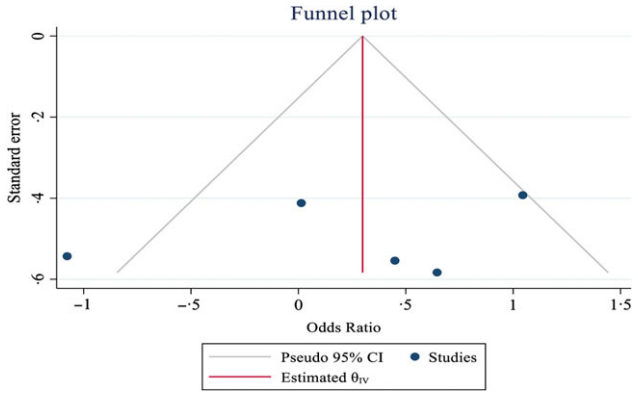

Fig. 8. Funnel plot of association between cranberry and Helicobacter pylori eradiction.

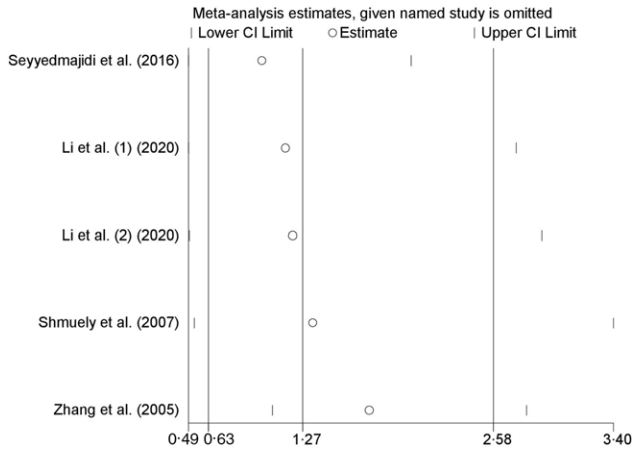

Fig. 9. The sensitivity analysis plot for detecting the influence of per included studies on the pooled estimate.

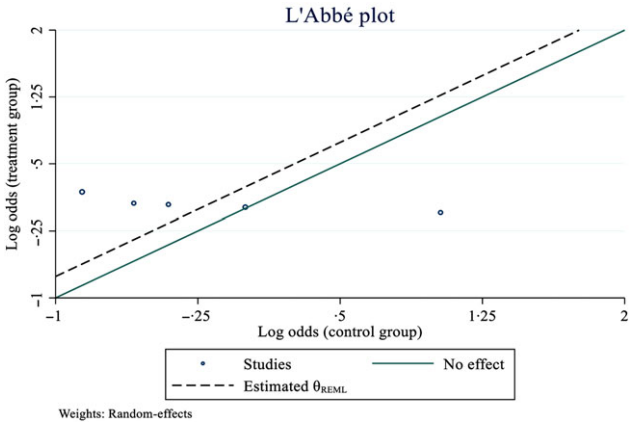

Fig. 10. L'Abbe plot for Helicobacter pylori eradiction rate in both the treatment and the control groups.

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The authors declare that there are no conflicts of interest.

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