BMJ Open

Effect of polyphenol compounds on *Helicobacter pylori* eradication: a systematic review with meta-analysis

Qiuxiang Wang [1,2,3] Chengjiao Yao [4] Yilin Li,[1,2] Lihong Luo [1,2] Fengjiao Xie [1,2] Qin Xiong [1,2] Peimin Feng[2]

To cite: Wang Q, Yao C, Li Y, *et al*. Effect of polyphenol compounds on *Helicobacter pylori* eradication: a systematic review with meta-analysis. *BMJ Open* 2023;**13**:e062932. doi:10.1136/bmjopen-2022-062932

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-062932).

Received 18 March 2022
Accepted 21 November 2022

[1]Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China
[2]Affiliated hospital of Chengdu university of traditional Chinese medicine, Chengdu, Sichuan, China
[3]Department of traditional Chinese medicine, The Central Hospital of Guangyuan City, Guangyuan, Sichuan, China
[4]Department of Geriatrics, Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan, China

Correspondence to
Peimin Feng; fpmvv@126.com

ABSTRACT

Objectives Polyphenol compounds are classified as organic compounds with phenolic units exhibiting a variety of biological functions. This meta-analysis aims to assess the efficacy and safety of polyphenol compounds (curcumin, cranberry, garlic, liquorice and broccoli) in eradicating *Helicobacter pylori*.

Design Systematic review and meta-analysis.

Methods Literature searches were conducted on PubMed, Embase, The Cochrane Library, Web of Science, Medline, Chinese National Knowledge Infrastructure database, Chinese Scientific Journal Database and Wan Fang database from inception to January 2022. All randomised controlled trials comparing polyphenol compounds with the placebo or used as an adjunct treatment are included in this meta-analysis.The treatment effect for dichotomous outcomes was assessed using risk ratio (RR), while for continuous outcomes, mean differences both with 95% CIs, were used. Subgroup analyses were carried out for different treatment schemes and polyphenol compound species.

Results 12 trials were included in the meta-analysis. The total eradication rate of *H.pylori* in the polyphenol compounds group was higher than in the group without polyphenol compounds. Statistical significance was also observed (RR 1.19, 95% CI 1.03 to 1.38, p=0.02). The most frequent adverse effects of polyphenol compounds included diarrhoea, headache and vomiting. However, there were no differences regarding side effects between the two groups (RR 1.47, 95% CI 0.83 to 2.58, p=0.18). In subgroup analyses, the *H.pylori* eradication rate regimens with polyphenols therapy was superior to that of regimens without polyphenols therapy in the polyphenols versus placebo subgroup (RR 4.23, 95% CI 1.38 to 12.95, p=0.01), polyphenols plus triple therapy versus triple therapy subgroup (RR 1.11, 95% CI 1.01 to 1.22, p=0.03).

Conclusion Polyphenol compounds can improve *H.pylori* eradication rates. Polyphenol compounds plus standard triple therapy can significantly improve the eradication. However, no evidence of a higher incidence of side effects could be found.

PROSPERO registration number CRD42022307477.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first meta-analysis of polyphenol efficacy and safety in eradicating *Helicobacter pylori*. The results indicate that polyphenols are conducive to *H. pylori* eradication.
⇒ We only analysed the eradication rate of *H. pylori* infection according to different treatment schemes and polyphenol compounds. We did not analyse the eradication rate based on polyphenol dose.
⇒ The symmetry of the funnel chart created by the 12 included studies is slightly poor, suggesting that there may be selection bias in the included literature. Most studies ignore the possible adverse reactions in the test, and safety observation should be improved.
⇒ The number of cases included in this meta-analysis is small, the quality of literature is low, and most do not describe specific random methods. The allocation concealment and blind evaluation are not perfect, which may affect the reliability of the research conclusions.
⇒ The results of subgroup analyses on different treatment schemes and species seem more inconclusive due to the fewer studies that could be included. We cannot determine the polyphenol contents of each food before and after the eradication period from each manuscript included in the analysis. This might work as a confounding factor. This confounding factor may have an impact on the final result.

INTRODUCTION

Helicobacter pylori has gained widespread attention for nearly 40 years since its identification by Marshall and Warren in 1984.[1] *H. pylori* is a spiral-shaped Gram-negative, microaerophilic bacterium that colonises the gastric mucosa.[2] *H. pylori* is usually acquired in childhood and can last a lifetime.[3] It was first explicitly formulated in the Kyoto Global Consensus Report that *H.pylori* gastritis should be considered an infectious disease regardless of whether the affected individual has any symptoms, complications or subsequent illnesses.[4] *H. pylori* has been classified as a group 1 carcinogen by the International Agency for Research on Cancer.[5] *H. pylori* infection is considered the leading cause of gastric cancer.[6]

More than half the world's population is infected with *H. pylori*.[2] The prevalence of *H. pylori* varies significantly between regions and countries.[7] Africa has the highest prevalence (79.1%), followed by Latin America and the Caribbean (63.4%) and Asia (54.7%). In contrast, *H.pylori* prevalence is lowest in Northern America (37.1%) and Oceania (24.4%).[7] The global prevalence of *H.pylori* is similar between genders, with 42.7% in women and 46.3% in men,[8] and approximately 20% of those infected will develop the disease.[9] The pooled *H. pylori* prevalence was 44.2% in mainland China, with an estimated 589 million people infected.[10] Furthermore, according to recent epidemiological data, the recurrence rate of *H.pylori* has increased over the past decade, and it remains a complex global public health problem that places a significant socioeconomic burden on the healthcare system.[11] The recurrence rate of *H.pylori* increases with time after eradication and varies by region, gender and eradication methods.[11] Therefore, it is critical to identify an effective regimen in this era of increasing antibiotic resistance. New approaches, such as polyphenol compounds, are being tested to enhance *H. pylori* eradication rates.

Polyphenol compounds are classified as organic compounds having phenolic units that display an array of biological functions. Polyphenol substances (eg, curcumin, cranberry, garlic, liquorice and broccoli) with potent antioxidant and anti-inflammatory properties can modulate key signalling molecules of enormous pharmacological interest.[12] Polyphenols may contribute to gastrointestinal health, as these bioactive compounds can inhibit *H.pylori* proliferation.[13] Several studies indicate that these polyphenol compounds positively affect *H. pylori* eradication.[14–21] However, several experimental and clinical studies have shown different results.[22 23] There are no known meta-analyses concerning the effects of polyphenol compounds on *H.pylori* infection. Therefore, we performed a meta-analysis of randomised controlled trials (RCTs) to evaluate the effect of polyphenol compounds on the eradication rate of *H. pylori* infection.

MATERIALS AND METHODS

Search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines[24] and was registered in PROSPERO. A systematic search was performed in the following eight databases with a restriction of time from inception to January 2022 to filter the eligible studies: PubMed, Embase, The Cochrane Library, Web of Science, Medline, Chinese National Knowledge Infrastructure database (CNKI), Chinese Scientific Journal Database (VIP) and Wan Fang database. The following search keywords were used: [*Helicobacter pylori*] or [*Helicobacter nemestrinae*] or [*Campylobacter pylori*] or [*Campylobacter pylori subsp. pylori*] or [*Campylobacter pyloridis*]; [Polyphenols] or [Curcumin] or [Vaccinium macrocarpon] or [Garlic] or [Glycyrrhiza] or [Brassica]; and [Randomised controlled trial] or [Clinical Trials, Randomized]or[Trials, Randomized Clinical]or[Controlled Clinical Trials, Randomized]. We considered the PubMed-specific search strategy a typical example, and the specific retrieval steps are shown in box 1. We also searched journal articles, conference papers and academic papers. The whole process of research selection is shown in figure 1.

Box 1 Search strategy in PubMed database

Search items
#1 ("Polyphenols"[(Mesh])) OR ((Polyphenol) OR (Provinols))
#2 ("Curcumin"[(Mesh])) OR (((((('1,6-Heptadiene-3,5-dione, 1,7-bis(4-hydroxy-3-methoxyphenyl)-, (E,E)-') OR (Turmeric Yellow)) OR ('Yellow, Turmeric')) OR (Curcumin Phytosome)) OR ('Phytosome, Curcumin')) OR (Diferuloylmethane)) OR (Mervia))
#3 ("Vaccinium macrocarpon"[(Mesh])) OR ((((Vaccinium macrocarpons) OR ('macrocarpon, Vaccinium')) OR (Cranberry)) OR (Cranberries))
#4 ("Garlic"[(Mesh])) OR (Allium sativum)
#5 ("Glycyrrhiza"[(Mesh])) OR (((((Liquorice) OR (Liquorices)) OR (Licorice)) OR (Licorices)) OR (Glycyrrhiza glabra))
#6 ("Brassica"[(Mesh])) OR (((((((Brussel Sprout) OR (Collard Green)) OR (Collard Greens)) OR (Kale)) OR (Cauliflower)) OR (Broccoli)) OR (Cabbage)) OR (Cabbages))
#7 #1or #2 or #3or #4 or #5 or #6
#8 ("*Helicobacter pylori*"[(Mesh])) OR ((((*Helicobacter nemestrinae*) OR (*Campylobacter pylori*)) OR ('*Campylobacter pylori subsp. pylori*')) OR (*Campylobacter pyloridis*))
#9 ("RandomizedRandomised Controlled Trial" [(Publication Type])) OR (((Clinical Trials, RandomizedRandomised[Title/Abstract]) OR (Trials, RandomizedRandomised Clinical[Title/Abstract])) OR (Controlled Clinical Trials, RandomizedRandomised[Title/Abstract]))
#10 #7 and #8 and #9

Study selection (inclusion and exclusion criteria)

Two independent reviewers (QW and CY) reviewed the initial search results. The following criteria were used for literature selection: (1) articles published in English or Chinese; (2) adults infected with *H. pylori* with/without *H. pylori*-related disease, including functional dyspepsia, gastritis and ulcers. The diagnosis of *H. pylori* infection was based on positive histology, rapid urease tests, urease breath tests or *H. pylori* stool antigen test; (3) articles that assessed the efficacy of polyphenol compounds in *H.pylori* eradication; (4) the intervention of the treatment group comprised of polyphenols alone or in combination with *H. pylori* eradication therapy. The control group received just the placebo without polyphenol compounds, or *H.pylori* eradication therapy; (5) the eradication rates and/or side effects data were available; (6) the study design consisted of RCTs; (7) the polyphenol compounds were restricted to curcumin, cranberry, garlic, liquorice and broccoli. The exclusion criteria included: (1) duplicate articles or evaluation of the same samples; (2) articles published as observational studies, narrative reviews, basic researches, meta-analyses, retrospective studies, case reports or conference presentations; (3) use of oral antibiotics and/or proton pump inhibitors (PPIs) and/or H2-antagonists during the 2 weeks before intake of the

study product; (4) extraction of polyphenols from other sources, such as tea, coffee, cocoa, wine, etc.

Data extraction

Two reviewers (FX and QX) independently extracted data from the included studies using a predesigned data extraction tool. Any disagreements were resolved by negotiation and discussion. Any additional disagreements were arbitrated by a third reviewer (PF). The following information was extracted from each included study: the first author's name, publication year, location, number of patients, diagnostic methods for testing *H.pylori* infection before enrolling and after completing the study, polyphenol compounds group regimen, control group regimen, the time test for *H. pylori* eradication, eradication rate as the primary outcome and side effect rate as the secondary outcome.

Quality appraisal

Two authors (LL and YL) independently evaluated the risk of bias of each included article using the Cochrane Handbook for Systematic Reviews of Interventions.[25] The methodologic quality was evaluated based on the following seven aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting and other biases. The risks were classified as low, high or unclear using a graphical representation. The quality assessment of each paper is shown in table 1.

Statistical analysis

Meta-analysis and statistical analysis were performed using RevMan software (V.5.3.0). The results were presented using the risk ratio (RR) with 95% CIs for dichotomous data. The mean difference with 95% CIs was used to present the results for continuous data. P<0.05 was considered statistically significant. Heterogeneity among studies was evaluated via χ^2 tests and the inconsistency statistic. I^2>50% and/or p<0.1 indicated significant heterogeneity. The fixed-effects model (Mantel-Haenszel) was used to analyse the data if there was no heterogeneity, while the random effects model was used if I^2>50%.[26] Subgroup analyses were conducted based on different treatment schemes and polyphenol compound species.

Patient and public involvement

No patient was involved.

RESULTS

Study selection and study characteristics

The literature search yielded 1178 articles, of which 569 were excluded as duplicates and 492 by title or abstract. The full texts of the remaining 117 articles were reviewed. Of these articles, 65 were unrelated, and 37 were basic research, systematic reviews or meta-analyses. One trial was excluded because it was conducted on children and two studies were not RCTs. A total of 12 RCTs with 1251 participants (624 from the polyphenol compounds group and 627 from the control group) were finally included. A flowchart of the article screening and selection processes is shown in figure 1. Eight studies[27–34] were conducted in Iran, two[18 35] in China, and the remaining studies were conducted in Israel[36] and India,[37] respectively. These studies were published between 2005 and 2021. All the studies were RCTs. Of the 12 studies, two studies[27 28] evaluated the efficacy of curcumin in eradicating *H.pylori*, four studies[18 29 35 36]evaluated the efficacy of cranberry, four studies[30–32 37] assessed the efficacy of liquorice, one study[34] evaluated the efficacy of garlic, and one study[33] assessed the efficacy of broccoli in eradicating *H.pylori*. The characteristics of each included study are summarised in table 2.

Table 1 Risk of bias of the included randomised controlled trials

Author/reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Judaki *et al*[27]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Khonche *et al*[28]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Shmuely *et al*[36]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Zhang *et al*[18]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Li *et al*[35]	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Seyyedmajidi *et al*[29]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Puram *et al*[37]	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Hajiaghamohammadi *et al*[30]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Rahnama *et al*[31]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Momeni *et al*[32]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Mirmiran *et al*[33]	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Hekmatdoost *et al*[34]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk

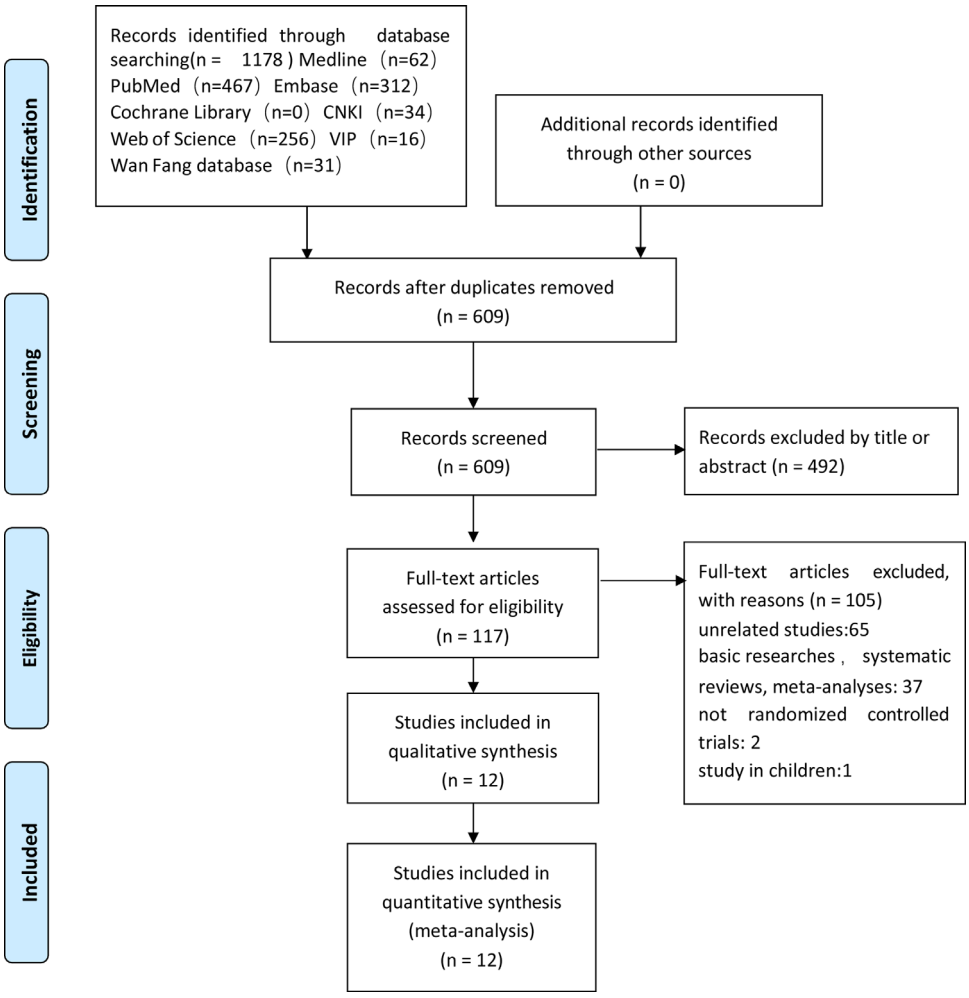

Figure 1 Flow diagram of search method and study selection. CNKI, China National Knowledge Infrastructure; VIP, Chinese Scientific Journal database.

Risk of bias

The Cochrane risk of bias assessment tool was used to evaluate the quality of the included studies.[25] The methodological quality of the included trials was generally poor. In random sequence generation, three trials[33 35 37] used proper generation methods with a low risk of bias, and the random number sequences were generated by either computer software or a sealed envelope. However, nine trials[18 27–32 34 36] did not clearly describe the randomisation procedure. Methods for double-blind were described by seven of the studies.[18 28 31 32 35–37] One study[33] described allocation concealment methods as a sealed envelope. Other studies have not described allocation concealment methods. Complete outcome data were reported by 12 studies. All studies had a low risk of selective reporting bias. All studies had an unclear risk of other biases.

RESULTS

Trial description

Among the 12 enrolled studies, three studies[18 35 37] compared the effects of polyphenols with placebo on the eradication rate of *H.pylori* infection; six studies[27–30 33 36] compared the effects of polyphenols along with triple therapy on the eradication rate of *H.pylori* infection; two studies[31 32] compared the effects of polyphenol plus triple therapy with bismuth triple therapy; one study[34] compared the effects of polyphenols plus quadruple regimen with quadruple regimen plus placebo on the eradication rate of *H.pylori* infection.

Primary outcomes

H. pylori eradication rate

Among the total cases, 624 patients were placed in the experimental group and 627 in the control group (figure 2). The Mantel-Haenszel random-effects model was used due to high heterogeneity (I^2=68%, p<0.01). For therapy with and without polyphenol compounds, the crude *H. pylori* eradication rate was 62.7% and 50.1%, respectively. The eradication efficacy of treatment with polyphenol compounds was higher than treatment without polyphenol compounds. Statistical significance was also observed (RR 1.19, 95% CI 1.03 to 1.38, p=0.02).

Secondary outcomes

Side effects

Among the 12 studies, three studies[28 32 37] provided information regarding side effects. During one study,[32] no

Table 2 The characteristics of each included study

Author/reference	Country	Number of patients (T/C)	Test for confirming *H. pylori* infection	Polyphenol compounds group	Control group	Outcomes
Judaki *et al*[27]	Iran	50/50	14C-UBT HpSAg	Curcumin 700 mg tid 4w plus control group therapy	Omeprazole 20 mg, bid, 1w amoxicillin 1 g, bid, 1w metronidazole 800 mg, bid, 1w	Eradication of *H.pylori*
Khonche *et al*[28]	Iran	30/30	UBT	Clarithromycin 500 mg, bid, 2w amoxicillin 1 g, bid, 2w pantoprazole 40 mg, bid, 2w curcumin 500 mg, qd, 2w	Clarithromycin 500 mg, bid, 2w amoxicillin 1 g, bid, 2w pantoprazole 40 mg, bid, 2w placebo qd, 2w	Eradication of *H. Pylori* side effects
Shmuely *et al*[36]	Israel	89/88	13C-UBT	Omeprazole 20 mg, bid, 1w amoxicillin 1 g, bid,1w clarithromycin 500 mg, bid, 1w cranberry juice 250 mL, bid, 2w	Omeprazole 20 mg, bid,1w amoxicillin1 g, bid, 1w clarithromycin 500 mg, bid, 1w placebo beverage 250 mL, bid, 2w	Eradication of *H. Pylori*
Zhang *et al*[18]	China	97/92	13C-UBT	Cranberry juice,250 mL, bid,90d	Placebo, 250 mL, bid, 90d	Eradication of *H. Pylori*
Li *et al* [35]	China	65/68	13C-UBT	Cranberry juice 240 mL, bid, 8w	Placebo juice 240 mL, bid, 8w	Eradication of *H. Pylori*
Seyyedmajidi *et al*[29]	Iran	100/100	13C-UBT Histology	Cranberry capsules,500 mg, bid 2w plus control group therapy	Lansoprazole 30 mg, bid, 2w amoxicillin 1 g, bid, 2 w clarithromycin 500 mg, bid,2w	Eradication of *H. Pylori*
Puram *et al*[37]	India	50/50	13C-UBT HpSAg	GutGard 150 mg, qd, 60d	Placebo, 150 mg, qd, 60d	Eradication of *H. Pylori* side effects
Hajiaghamohammadi *et al*[30]	Iran	54/56	HpSAg	Liquorice 380 mg, bid 2w plus control group therapy	Clarithromycin 500 mg, bid, 2w amoxicillin 1 g, qd, 2w omeprazole 20 mg, bid, 2w plus omeprazole 20 mg, qd, 4w	Eradication of *H. Pylori*
Rahnama *et al*[31]	Iran	20/20	UBT	Amoxicillin 500 mg, tid,15d metronidazole 250 mg, qid, 15d omeprazole 20 mg, bid, 30 d liquorice 250 mg, tid 30d	Amoxicillin 500 mg, tid, 15d metronidazole 250 mg, qid,15d omeprazole 20 mg, bid, 30 d bismuth sub nitrate 500 mg, tid, 30 d	Eradication of *H. Pylori*
Momeni *et al*[32]	Iran	30/30	UBT	Metronidazole 500 mg bid 2w amoxicillin 1 g, bid, 2w omeprazole 20 mg, bid, 2w liquorice 380 mg, bid, 2w	Metronidazole 500 mg, bid, 2w amoxicillin 1 g, bid, 2w omeprazole 20 mg, bid, 2w bismuth subsalicylate, 262 mg, bid 2w	Eradication of *H. Pylori* side effects
Mirmiran *et al*[33]	Iran	24/28	HpSAg	Broccoli sprouts powder 6 g, qd, 4w plus control group therapy	Omeprazole 20 mg, bid, 2w clarithromycin 500 mg, bid, 2w amoxicillin 1 g, bid, 2w	Eradication of *H. Pylori*
Hekmatdoost *et al*[34]	Iran	15/15	UBT	Garlic powder 4 g, qd, 8w omeprazole 20 mg, bid, 2w amoxicillin 1 g, bid, 2w Bismuth 1.5 g bid, 2w metronidazole 500 mg, bid, 2w	Placebo 4 g, qd, 8w omeprazole 20 mg, bid, 2w amoxicillin 1 g, bid, 2w Bismuth 1.5 g bid, 2w metronidazole 500 mg, bid, 2w	Eradication of *H. Pylori*

bid, twice a day; C, control group; HpSAg, stool antigen test; qd, once a day; qid, four times a day; T, treatment group; tid, three times a day; UBT, urease breath test; w, week.

side effects or interactions (such as severe hypertension, muscular weakness or diarrhoea) were reported that led to treatment discontinuation. The side effect rates were observed in two RCTs,[28 37] including 160 patients. The most frequent adverse reactions were diarrhoea, headache and vomiting, followed by mild body temperature, nausea, throat pain and mild cold and cough. The side effect rate in the treatment group was 27.5%, while in the control group, it was 18.8%. There was no significant difference between these two groups (RR 1.47, 95% CI 0.83 to 2.58, p=0.18) (figure 3).

Subgroup analysis

Subgroup analysis of different treatment schemes

In the polyphenols versus placebo subgroup, the crude *H. pylori* eradication rate was 24.1% for polyphenols and 5.2% for placebo. The crude *H. pylori* eradication rate in the polyphenols plus triple therapy versus triple therapy

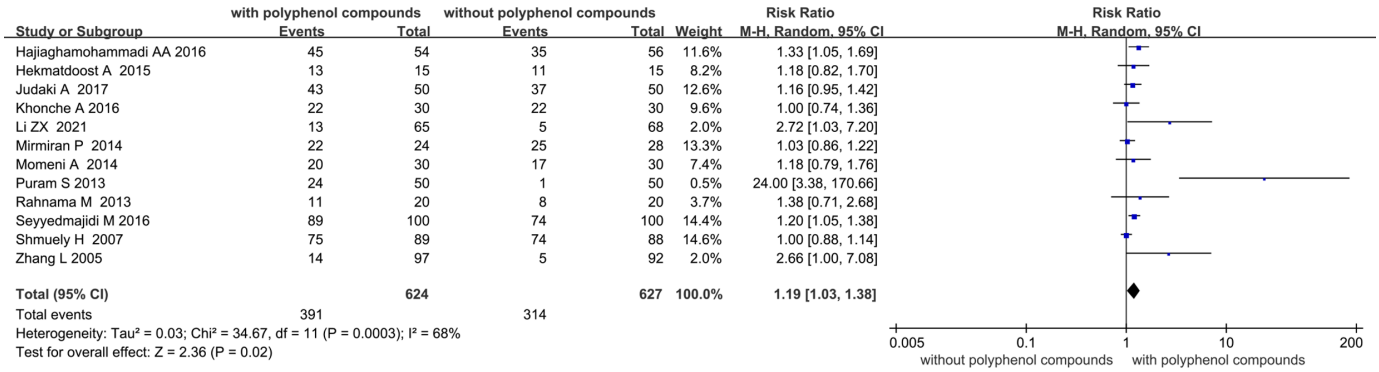

Figure 2 Forest plots for eradication rate comparison between polyphenol compounds groups and control groups.

subgroup was 85.3% and 75.9%, respectively. The crude *H. pylori* eradication rate in the polyphenols plus triple therapy versus bismuth triple therapy subgroups was 62% and 50%, respectively. In the polyphenols plus quadruple regimen versus quadruple regimen subgroups, the crude *H. pylori* eradication rate was 86.7% and 73.3%, respectively.

Figure 4 shows that the *H.pylori* eradication rate of regimens with polyphenols therapy was superior to that of regimens without polyphenol therapy in the polyphenols versus placebo subgroup (RR: 4.23, 95% CI 1.38 to 12.95, p=0.01) and the polyphenols plus triple therapy versus triple therapy subgroup (RR 1.11, 95% CI 1.01 to 1.22, p=0.03). No difference was observed between the polyphenols plus triple therapy and bismuth triple therapy subgroups (RR 1.23, 95% CI 0.87 to 1.73, p=0.25). In the polyphenols plus quadruple regimen versus quadruple regimen subgroups, no difference was observed between the two groups (RR 1.18, 95% CI 0.82 to 1.70, p=0.37).

Subgroup analysis of different kinds of polyphenols

The curcumin therapy subgroup consisted of two studies.[27 28] The cranberry therapy subgroup included four studies.[18 29 35 36] The liquorice therapy subgroup included four studies,[30–32 37] while one study[34] was enrolled as the garlic therapy subgroup and one[33] as the broccoli therapy subgroup.

Figure 5 displays that the crude *H. pylori* eradication rate in the curcumin subgroup was 81.3% for the treatment group and 73.8% for the control group. The crude *H. pylori* eradication rate in the cranberry subgroup was 54.4% and 45.4% for the treatment and control groups, respectively. The crude *H. pylori* eradication rate in the liquorice subgroup was 64.9% and 39.1% for the treatment and control groups, respectively. The crude *H. pylori* eradication rate in the garlic subgroup was 86.7% and 73.3% for the treatment and control groups, respectively. The crude *H. pylori* eradication rate in the broccoli subgroup was 91.7% for the treatment group and 89.3% for the control group. However, there was no statistical significance in the subgroup analysis based on different polyphenol compounds (curcumin: (RR 1.11, 95% CI 0.94 to 1.31, p=0.21) cranberry: (RR 1.24, 95% CI 0.94 to 1.64, p=0.13) liquorice: (RR 1.57, 95% CI 0.89 to 2.78, p=0.12) garlic: (RR 1.18, 95% CI 0.82 to 1.70, p=0.37) broccoli: (RR 1.03, 95% CI 0.86 to 1.22, p=0.77)).

Sensitivity analysis

By removing one study at a time, none of the studies significantly altered the pooled risk of the *H. pylori* eradication rates, indicating the results of this study were reliable.

Publication bias

The funnel plot obtained by an intentional analysis of eradication rates revealed a slightly asymmetrical distribution (figure 6). Visual inspection of the funnel plot suggested that publication bias existed.

DISCUSSION

Summary of evidence

We found that the eradication rate of *H. pylori* was higher for eradication therapy with polyphenol compounds than without polyphenol compounds. These results showed a possible beneficial effect of polyphenol compounds on eradicating *H.pylori*. Furthermore, no evidence for an increased rate of side effects could be found. In the subgroup analysis, the three studies[18 35 37] involving polyphenols showed a higher eradication rate than the

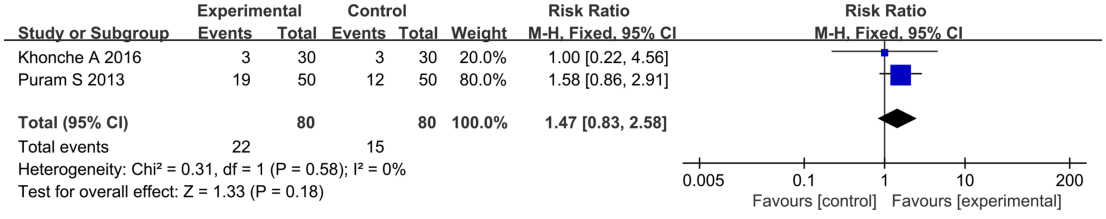

Figure 3 Forest plots for the incidence of side effects comparison between polyphenol compounds and control groups.

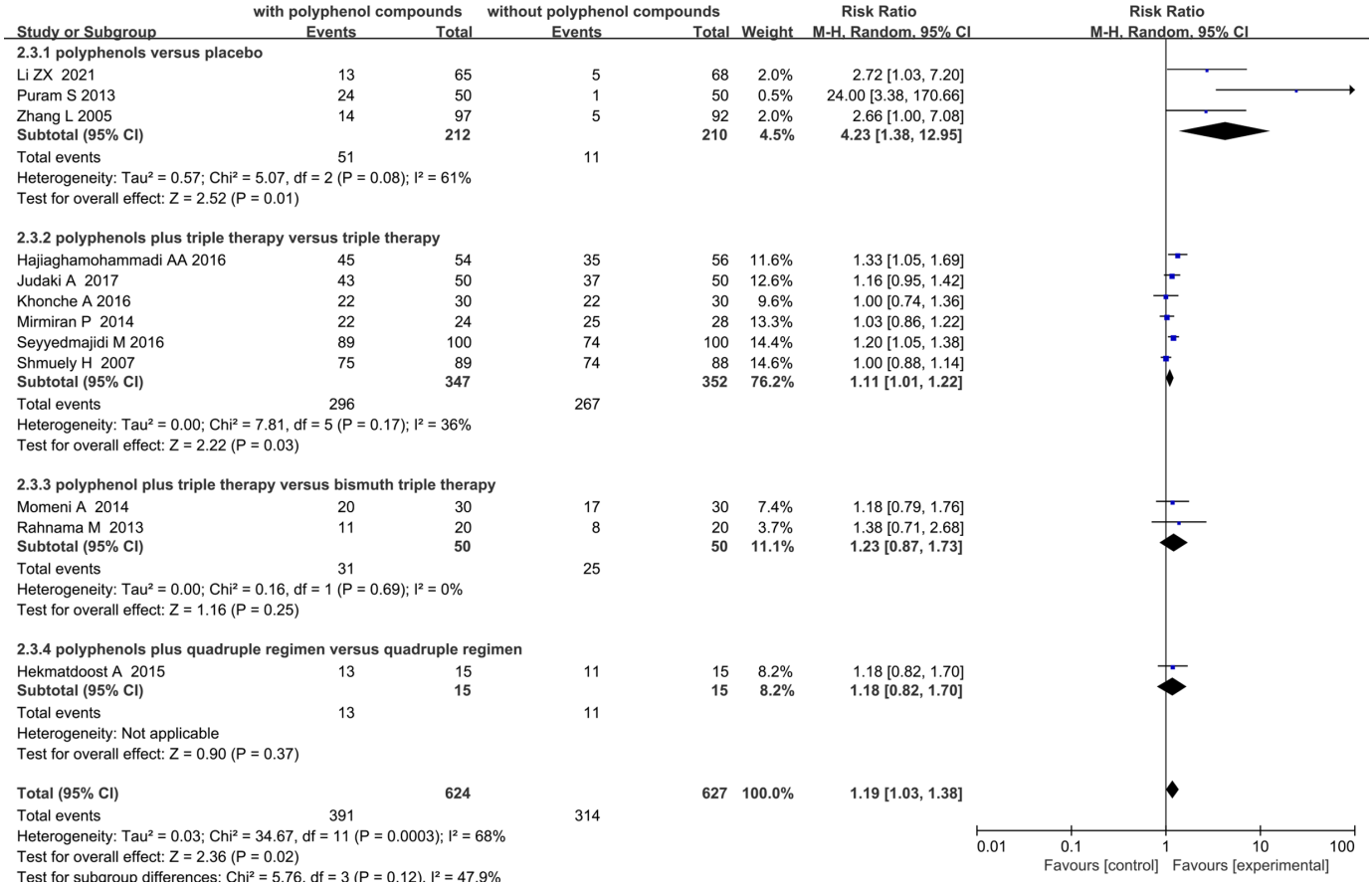

Figure 4 Subgroup analysis for different treatment schemes between the two groups.

placebo group. The six studies[27–30 33 36] with polyphenols plus triple therapy showed a higher eradication than the triple therapy group. However, there were no differences between the polyphenols plus triple therapy and bismuth triple therapy subgroups, nor between the polyphenols plus quadruple regimen and the quadruple regimen subgroups. Finally, we analysed the efficacy of eradication rates according to the polyphenol compound species. However, no significant differences existed between these five subgroups.

The harmfulness of *H. pylori* and the current treatment status

Infection with *H.pylori* is a major pathogenic factor for superficial gastritis, chronic atrophic gastritis, duodenal or gastric ulcers and gastric mucosa-associated lymphoid tissue lymphoma.[38] It has also been linked with several extra-digestive diseases such as atherosclerosis,[39] coronary heart disease,[40] iron deficiency anaemia,[41] idiopathic thrombocytopenic purpura,[42] vitamin B12 deficiency,[43] non-alcoholic fatty liver disease,[44] metabolic syndrome,[45] diabetes mellitus,[46] cerebrovascular disease,[47] Alzheimer's disease,[48] Parkinson's disease,[49] childhood asthma,[50] chronic obstructive pulmonary disease,[51] chronic urticaria,[52] rosacea[53] and osteoporosis.[54] *H. pylori* eradication is required for managing *H. pylori*-related complications.

The efficacy of standard 1-week triple therapy containing clarithromycin and either metronidazole or amoxicillin combined with a PPI has decreased dramatically, with eradication rates as low as 50%–70%.[55] Antibiotic resistance and patient compliance are the major causes of this decline.[56] Bismuth-containing quadruple therapy is now recommended as the main empirical therapy in regions with high clarithromycin and metronidazole resistance (>15%).[57] Concomitant, sequential and hybrid therapies are also recommended for treating *H. pylori* infection.[58] However, there are currently few, if any, regimens consistently achieve eradication rates exceeding 90%.[59]

Our research results indicate that polyphenol compounds can significantly improve *H. pylori* eradication rates; it might be more effective during polyphenol treatment combined with standard triple therapy. Our findings support that polyphenol compounds can be used as a promising adjuvant therapy to eradicate *H.pylori*, which is of great clinical importance in the era of antibiotic resistance.

Other studies supporting the findings

Polyphenols possess numerous pharmacological and therapeutic properties, including antioxidant and anti-inflammatory activities.[60] The main attribute of polyphenols and their metabolites is their antioxidant action by targeting immune cells and activating different signalling pathways that modify interleukins, cyclooxygenase, nitric oxide synthase and other inflammatory responses.[60] The yellow pigment curcumin (diferuloylmethane) is a key poly-phenolic molecule found in turmeric root.[61]

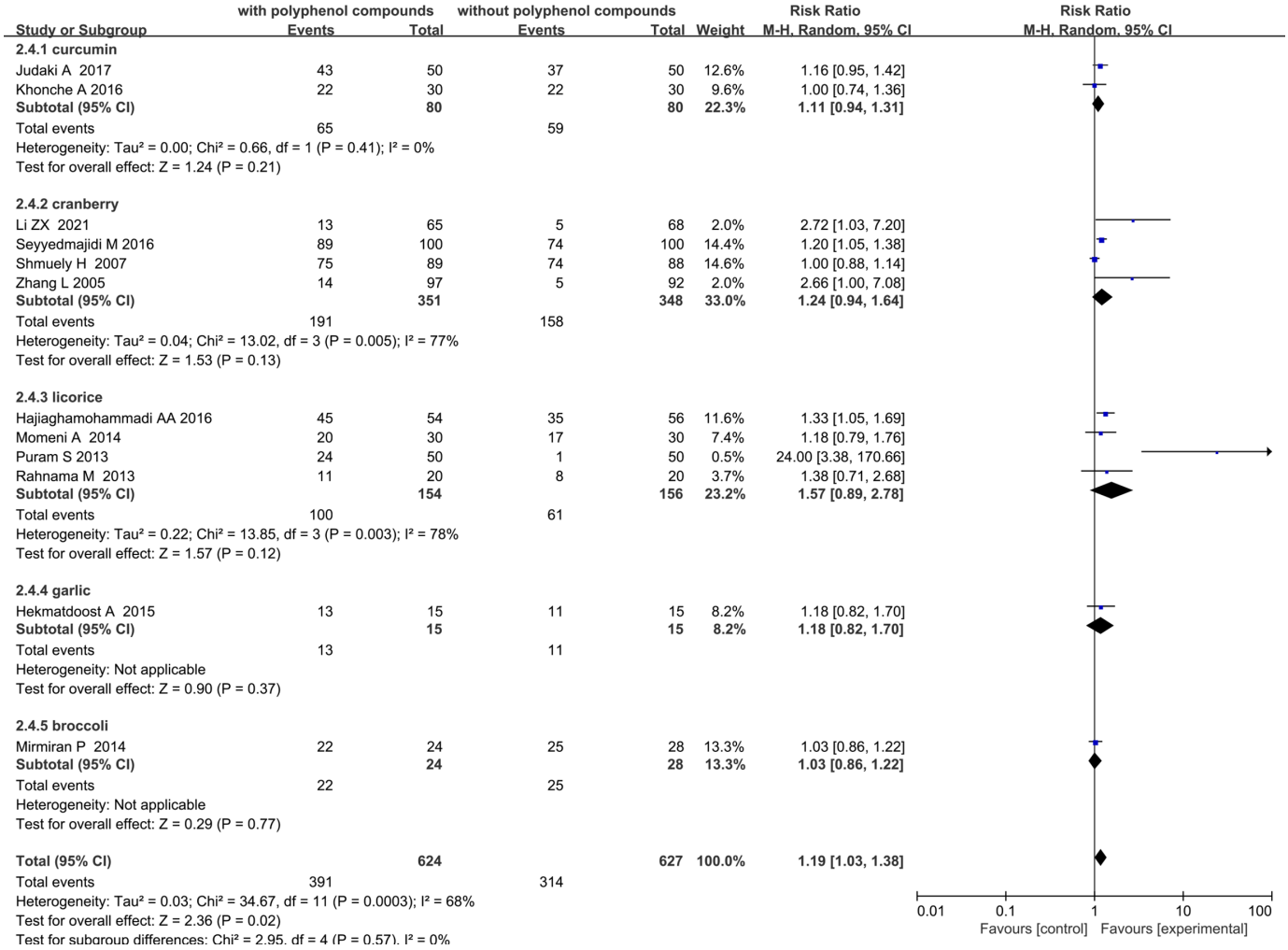

Figure 5 Subgroup analysis for *H. pylori* eradication rate in different species of polyphenol compounds.

Curcumin exhibits anti-inflammatory, antioxidant, anticancer, antiviral and neurotrophic activities.[62] Its effects on *H. pylori* infection have been repeatedly confirmed in animal and human models.[14–17] It has been demonstrated in animal experiments that curcumin treatment exhibited a significant anti-inflammatory effect in *H. pylori*-infected gastric mucosa.[63] Several studies have shown

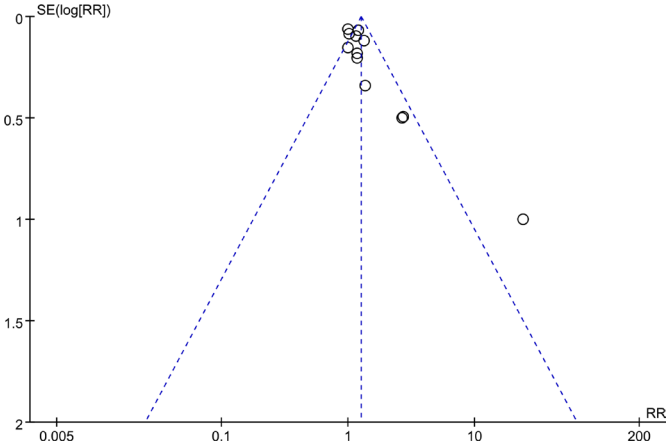

Figure 6 Funnel plot of the eradication rates of the included studies.

that cranberry juice constituents inhibit the adhesion of numerous microbial pathogens, including *H.pylori*, *E.coli*, oral bacteria and influenza virus.[36] Mechanisms of cranberry's suppression of *H. pylori* may be due to phenolic compounds found in the fruit.[35] In a clinical trial conducted on colonised Chinese adults, cranberry juice eradicated *H.pylori* in 14.4% of subjects.[18] Cranberry extract inhibited *H. pylori* proliferation in vitro, suggesting that polyphenols are responsible for this action. The morphological analysis revealed that cranberry induces *H. pylori* to develop a coccoid form, inhibiting its growth.[64] Garlic is rich in polyphenols, and previous in vitro studies have shown that Garlic oil may be useful as an alternative treatment against *H.pylori*.[19]

Several studies have shown that extracts from raw garlic or garlic powder tablets maintain in vitro activity against *H. pylori*.[65 66] Moreover, licorice (liquorice or sweet wood) has been shown to have anti-*H.pylori* effects.[20] Glycyrrhiza glabra showed anti-*H. pylori* activity in vitro and its possible mechanism of acts against *H.pylori* include inhibiting protein synthesis, DNA gyrase and dihydrofolate reductase.[67] Another study showed that an aqueous extract of glycyrrhiza glabra significantly inhibited *H.pylori* adhesion to human stomach tissue.[68] Furthermore, an

in vivo approach to evaluating the efficacy of fresh broccoli sprouts demonstrated that oral treatment of C57BL mice with broccoli sprouts resulted in a reduction in *H.pylori* colonisation.[21] A study reported that broccoli sprout extract containing sulforaphane prevented lipid peroxidation in the gastric mucosa and may play a cytoprotective role in *H.pylori*-induced gastritis.[69]

The appropriate doses of these polyphenol compounds for eradicating *H. pylori*

Two articles about curcumin were included in this meta-analysis. After carefully reading these two articles, we discovered that curcumin (700mg,three times a day, 4 weeks) could be a useful supplement of triple therapy to eradicate H.pylori.[27 28] The meta-analysis included four articles about cranberries. These findings suggest that cranberries can be used as a daily diet supplement (240mL, two times per day, 8 weeks) to help suppress *H.pylori* infection.[18 35] Furthermore, adding cranberry (500mg, two times per day, 2 weeks) to lansoprazole, clarithromycin and amoxicillin triple therapy for *H. pylori* has a higher eradication rate than the standard regimen alone.[29] This meta-analysis included four studies about liquorice. One showed that GutGard (150mg, one time per day,60 days) is more effective than the placebo in treating *H.pylori*.[37] Furthermore, liquorice (380mg, two times per day, 2weeks) is commonly added to triple or quadruple schemes.[30–32] This meta-analysis included one study on garlic, which did not support a role for garlic in the treatment of *H.pylori* infection.[34] More relevant research articles must be included in the future to determine the effective dose of garlic to eradicate *H. pylori*. Furthermore, broccoli sprout powder (6g, one time per day,4weeks) plus standard triple therapy affect *H. pylori* eradication.[33]

CONCLUSION

In conclusion, current evidence suggests that polyphenol compounds (curcumin, cranberry, garlic, liquorice and broccoli) can improve eradication rates. Furthermore, polyphenol compounds combined with standard triple therapy for *H.pylori* infection can significantly improve eradication. However, no evidence for an increased rate of side effects could be found. Due to the low quality of the included studies, these results should be interpreted with caution. More large-scale, high-quality clinical trials should be conducted to provide a stronger, evidence-based foundation for guiding clinical medication.

Contributors QW conceptualised and designed the study, handled the meta-analysis software and wrote the first and final drafts of the manuscript. The search strategies were designed by QW and CY. The electronic search was conducted by QW, FX and QX. QW manually searched key journals. FX and QX extracted the data. The risk of bias was assessed by LL and LY, independently. QW and CY analysed and interpreted the data. PF arbitrated any disagreements in the process of meta-analysis. All authors have read and approved the final manuscript. QW and PF are the study guarantors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iDs
Qiuxiang Wang http://orcid.org/0000-0002-6316-8279
Chengjiao Yao http://orcid.org/0000-0002-7716-368X
Lihong Luo http://orcid.org/0000-0001-9055-1137
Fengjiao Xie http://orcid.org/0000-0003-4344-0973
Qin Xiong http://orcid.org/0000-0003-2846-7369

REFERENCES

1 Marshall B, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984;323:1311–5.
2 Ullah H, Di Minno A, Santarcangelo C, *et al*. Vegetable extracts and nutrients useful in the recovery from Helicobacter pylori infection: a systematic review on clinical trials. *Molecules* 2021;26:2272.
3 Wroblewski LE, Peek RM. Helicobacter pylori: a stealth assassin. *Trends Cancer* 2021;7:807–8.
4 Sugano K, Tack J, Kuipers EJ, *et al*. Kyoto global consensus report on *Helicobacter pylori* gastritis. *Gut* 2015;64:1353–67.
5 Rowland M. The continuing decline in the prevalence of Helicobacter pylori infection. *Lancet Child Adolesc Health* 2022;6:139–40.
6 Kawai S, Wang C, Lin Y, *et al*. Lifetime incidence risk for gastric cancer in the *Helicobacter pylori* -infected and uninfected population in Japan: A Monte Carlo simulation study. *Int J Cancer* 2022;150:18–27.
7 Hooi JKY, Lai WY, Ng WK, *et al*. Global prevalence of Helicobacter pylori infection: systematic review and meta-analysis. *Gastroenterology* 2017;153:420–9.
8 Sjomina O, Pavlova J, Niv Y, *et al*. Epidemiology of *Helicobacter pylori* infection. *Helicobacter* 2018;23:e12514.
9 Fontes LES, Martimbianco ALC, Zanin C, *et al*. N-Acetylcysteine as an adjuvant therapy for Helicobacter pylori eradication. *Cochrane Database Syst Rev* 2019;2:CD012357.
10 Ren S, Cai P, Liu Y, *et al*. Prevalence of *Helicobacter pylori* infection in China: A systematic review and meta-analysis. *J Gastroenterol Hepatol* 2022;37:464–70.
11 Zhao H, Yan P, Zhang N, *et al*. The recurrence rate of *Helicobacter pylori* in recent 10 years: A systematic review and meta-analysis. *Helicobacter* 2021;26:e12852.
12 Sarkar A, De R, Mukhopadhyay AK. Curcumin as a potential therapeutic candidate for *Helicobacter pylori* associated diseases. *WJG* 2016;22:2736–48.
13 Guerra-Valle M, Orellana-Palma P, Petzold G. Plant-based polyphenols: anti-Helicobacter pylori effect and improvement of gut microbiota. *Antioxidants* 2022;11:109.
14 De R, Kundu P, Swarnakar S, *et al*. Antimicrobial activity of curcumin against *Helicobacter pylori* Isolates from India and during infections in mice. *Antimicrob Agents Chemother* 2009;53:1592–7.
15 Ray AK, Luis PB, Mishra SK, *et al*. Curcumin oxidation is required for inhibition of Helicobacter pylori growth, translocation and phosphorylation of CAG a. *Front Cell Infect Microbiol* 2021;11:765842.
16 Larussa T, Gervasi S, Liparoti R, *et al*. Downregulation of interleukin-(IL-) 17 through enhanced indoleamine 2,3-Dioxygenase (IDO) induction by Curcumin: a potential mechanism of tolerance towards *Helicobacter pylori*. *J Immunol Res* 2018;2018:1–7.
17 Panahi Y, Karbasi A, Valizadegan G, *et al*. Effect of curcumin on severity of functional dyspepsia: a triple blinded clinical trial. *Adv Exp Med Biol* 2021;1308:119–26.
18 Zhang L, Ma J, Pan K, *et al*. Efficacy of cranberry juice on Helicobacter pylori infection: a double-blind, randomized placebo-controlled trial. *Helicobacter* 2005;10:139–45.

19 O'Gara EA, Maslin DJ, Nevill AM, *et al*. The effect of simulated gastric environments on the anti-Helicobacter activity of garlic oil. *J Appl Microbiol* 2008;104:1324–31.
20 Lee H-A, Kim J-Y, Kim J, *et al*. Anti-Helicobacter pylori activity of acomplex mixture of Lactobacillus paracasei HP7 including the extract of Perilla frutescens var. acuta and Glycyrrhiza glabra. *Lab Anim Res* 2020;36:40.
21 Yanaka A, Fahey JW, Fukumoto A, *et al*. Dietary sulforaphane-rich broccoli sprouts reduce colonization and attenuate gastritis in *Helicobacter pylori-infected* mice and humans. *Cancer Prevention Research* 2009;2:353–60.
22 Di Mario F, Cavallaro LG, Nouvenne A, *et al*. A curcumin-based 1-week triple therapy for eradication of Helicobacter pylori infection: something to learn from failure? *Helicobacter* 2007;12:238–43.
23 Nikbazm R, Rahimi Z, Moradi Y, *et al*. The effect of cranberry supplementation on *Helicobacter pylori* eradication in *H. pylori* positive subjects: a systematic review and meta-analysis of randomised controlled trials. *Br J Nutr* 2021:1–10.
24 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
25 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
26 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
27 Judaki A, Rahmani A, Feizi J, *et al*. Curcumin in combination with triple therapy regimes ameliorates oxidative stress and histopathologic changes in chronic gastritis-associated Helicobacter pylori infection. *Arq Gastroenterol* 2017;54:177–82.
28 Khonche A, Biglarian O, Panahi Y, *et al*. Adjunctive therapy with curcumin for peptic ulcer: a randomized controlled trial. *Drug Res* 2016;66:444–8.
29 Seyyedmajidi M, Ahmadi A, Hajiebrahimi S, *et al*. Addition of cranberry to proton pump inhibitor-based triple therapy for *Helicobacter pylori* eradication. *J Res Pharm Pract* 2016;5:248–51.
30 Hajiaghamohammadi AA, Zargar A, Oveisi S, *et al*. To evaluate of the effect of adding licorice to the standard treatment regimen of Helicobacter pylori. *Braz J Infect Dis* 2016;20:534–8.
31 Rahnama M, Mehrabani D, Japoni S, *et al*. The healing effect of licorice (Glycyrrhiza glabra) on Helicobacter pylori infected peptic ulcers. *J Res Med Sci* 2013;18:532–3.
32 Momeni A, Rahimian G, Kiasi A, *et al*. Effect of licorice versus bismuth on eradication of Helicobacter pylori in patients with peptic ulcer disease. *Pharmacognosy Res* 2014;6:341–4.
33 Mirmiran P, Bahadoran Z, Golzarand M, *et al*. A comparative study of broccoli sprouts powder and standard triple therapy on cardiovascular risk factors following H.pylori eradication: a randomized clinical trial in patients with type 2 diabetes. *J Diabetes Metab Disord* 2014;13:64.
34 Hekmatdoost A, Ghobeh M, Shaker-Hosseini R. The effect of garlic consumption on Helicobacter pylori treatment using urea breath Test : A randomized clinical trial. *J Nutr Sci Diet* 2015:21–7 URL:https://jnsd.tums.ac.ir/index.php/jnsd/article/view/4.
35 Li Z-X, Ma J-L, Guo Y, *et al*. Suppression of Helicobacter pylori infection by daily cranberry intake: a double-blind, randomized, placebo-controlled trial. *J Gastroenterol Hepatol* 2021;36:927–35.
36 Shmuely H, Yahav J, Samra Z, *et al*. Effect of cranberry juice on eradication of Helicobacter pylori in patients treated with antibiotics and a proton pump inhibitor. *Mol Nutr Food Res* 2007;51:746–51.
37 Puram S, Suh HC, Kim SU, *et al*. Effect of GutGard in the management of *Helicobacter pylori*: a randomized double blind placebo controlled study. *Evid Based Complement Alternat Med* 2013;2013:1–8.
38 Fischbach W, Malfertheiner P. Helicobacter pylori infection. *Deutsches Arzteblatt International* 2018;115:429–36.
39 Shi H, Li Y, Dong C, *et al*. *Helicobacter pylori* infection and the progression of atherosclerosis: a systematic review and meta-analysis. *Helicobacter* 2022;27:e12865.
40 Sun J, Rangan P, Bhat SS, *et al*. A meta-analysis of the association between *Helicobacter pylori* infection and risk of coronary heart disease from published prospective studies. *Helicobacter* 2016;21:11–23.
41 Hudak L, Jaraisy A, Haj S, *et al*. An updated systematic review and meta-analysis on the association between *Helicobacter pylori* infection and iron deficiency anemia. *Helicobacter* 2017;22:e12330.
42 Lee A, Hong J, Chung H, *et al*. Helicobacter pylori eradication affects platelet count recovery in immune thrombocytopenia. *Sci Rep* 2020;10:9370.
43 Gökışık MT, Uyar S. The role of Helicobacter pylori in vitamin-B_{12} deficiency due to metformin use. *Helicobacter* 2020;25:e12718.
44 Abdel-Razik A, Mousa N, Shabana W, *et al*. *Helicobacter pylori* and non-alcoholic fatty liver disease: A new enigma? *Helicobacter* 2018;23:e12537.
45 Kountouras J, Polyzos SA, Doulberis M, *et al*. Potential impact of Helicobacter pylori-related metabolic syndrome on upper and lower gastrointestinal tract oncogenesis. *Metabolism* 2018;87:18–24.
46 Kato M, Toda A, Yamamoto-Honda R, *et al*. Association between *Helicobacter pylori* infection, eradication and diabetes mellitus. *J Diabetes Investig* 2019;10:1341–6.
47 Shindler-Itskovitch T, Chodick G, Shalev V, *et al*. *Helicobacter pylori* infection and prevalence of stroke. *Helicobacter* 2019;24:e12553.
48 Beydoun MA, Beydoun HA, Elbejjani M, *et al*. *Helicobacter pylori* seropositivity and its association with incident all-cause and Alzheimer's disease dementia in large national surveys. *Alzheimer's & Dementia* 2018;14:1148–58.
49 McGee DJ, Lu X-H, Disbrow EA. Stomaching the possibility of a pathogenic role for Helicobacter pylori in Parkinson's disease. *J Parkinsons Dis* 2018;8:367–74.
50 den Hollander WJ, Sonnenschein-van der Voort AMM, Holster IL, *et al*. *Helicobacter pylori* in children with asthmatic conditions at school age, and their mothers. *Aliment Pharmacol Ther* 2016;43:933–43.
51 Sze MA, Chen Y-WR, Tam S, *et al*. The relationship between *Helicobacter pylori* seropositivity and COPD. *Thorax* 2015;70:923–9.
52 Kim HJ, Kim Y-J, Lee HJ, *et al*. Systematic review and meta-analysis: Effect of *Helicobacter pylori* eradication on chronic spontaneous urticaria. *Helicobacter*2019;24:e12661.
53 Yang X. Relationship between Helicobacter pylori and rosacea: review and discussion. *BMC Infect Dis* 2018;18:318.
54 Shih H-M, Hsu T-Y, Chen C-Y, *et al*. Analysis of patients with Helicobacter pylori infection and the subsequent risk of developing osteoporosis after eradication therapy: a nationwide population-based cohort study. *PLoS One* 2016;11:e0162645.
55 Fallone CA, Chiba N, van Zanten SV, *et al*. The Toronto consensus for the treatment of Helicobacter pylori infection in adults. *Gastroenterology* 2016;151:51–69.
56 Ranjbar R, Chehelgerdi M. Genotyping and antibiotic resistance properties of *Helicobacter pylori* strains isolated from human and animal gastric biopsies. *Infect Drug Resist* 2018;11:2545–54.
57 Liu WZ, Xie Y, Lu H, *et al*. Fifth Chinese national consensus report on the management of *Helicobacter pylori* infection. *Helicobacter* 2018;23:e12475.
58 Chey WD, Leontiadis GI, Howden CW, *et al*. Correction: ACG clinical guideline: treatment of Helicobacter pylori infection. *Am J Gastroenterol* 2018;113:1102.
59 Li B-Z, Threapleton DE, Wang J-Y, *et al*. Comparative effectiveness and tolerance of treatments for Helicobacter pylori: systematic review and network meta-analysis. *BMJ* 2015;351:h4052.
60 Khan H, Sureda A, Belwal T, *et al*. Polyphenols in the treatment of autoimmune diseases. *Autoimmun Rev* 2019;18:647–57.
61 Irving GRB, Karmokar A, Berry DP, *et al*. Curcumin: the potential for efficacy in gastrointestinal diseases. *Best Pract Res Clin Gastroenterol* 2011;25:519–34.
62 Lopresti AL. The problem of curcumin and its bioavailability: could its gastrointestinal influence contribute to its overall health-enhancing effects? *Advances in Nutrition* 2018;9:41–50.
63 Santos A, Lopes T, Oleastro M, *et al*. Curcumin inhibits gastric inflammation induced by Helicobacter pylori infection in a mouse model. *Nutrients* 2015;7:306–20.
64 Matsushima M, Suzuki T, Masui A, *et al*. Growth inhibitory action of cranberry on *Helicobacter pylori*. *J Gastroenterol Hepatol* 2008;23:S175–80.
65 Cañizares P, Gracia I, Gómez LA, *et al*. Optimization of Allium sativum solvent extraction for the inhibition of in vitro growth of Helicobacter pylori. *Biotechnol Prog* 2002;18:1227–32.
66 Lawson* LD, Wang ZJ, Papadimitriou D. Allicin release under simulated gastrointestinal conditions from garlic powder tablets employed in clinical trials on serum cholesterol. *Planta Med* 2001;67:13–18.
67 Asha MK, Debraj D, Prashanth D'souza, *et al*. In vitro anti-Helicobacter pylori activity of a flavonoid rich extract of Glycyrrhiza glabra and its probable mechanisms of action. *J Ethnopharmacol* 2013;145:581–6.
68 Wittschier N, Faller G, Hensel A. Aqueous extracts and polysaccharides from liquorice roots (Glycyrrhiza glabra L.) inhibit adhesion of Helicobacter pylori to human gastric mucosa. *J Ethnopharmacol* 2009;125:218–23.
69 Chang YW, Jang JY, Kim YH, *et al*. The effects of broccoli sprout extract containing sulforaphane on lipid peroxidation and Helicobacter pylori infection in the gastric mucosa. *Gut Liver* 2015;9:486–93.