

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

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## 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.

## INTRODUCTION

*Helicobacter pylori* has gained widespread attention for nearly 40 years since its identification by Marshall and Warren in 1984.<sup>1</sup>

## 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.

*H. pylori* is a spiral-shaped Gram-negative, microaerophilic bacterium that colonises the gastric mucosa.<sup>2</sup> *H. pylori* is usually acquired in childhood and can last a lifetime.<sup>3</sup> 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.<sup>4</sup> *H. pylori* has been classified as a group 1 carcinogen by the International Agency for Research on Cancer.<sup>5</sup> *H. pylori* infection is considered the leading cause of gastric cancer.<sup>6</sup>

More than half the world's population is infected with *H. pylori*.<sup>2</sup> The prevalence of *H. pylori* varies significantly between regions and countries.<sup>7</sup> 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%).<sup>7</sup> The global prevalence of *H. pylori* is similar between genders, with 42.7% in women and 46.3% in men,<sup>8</sup> and approximately 20% of those infected will develop the disease.<sup>9</sup> The pooled *H. pylori* prevalence was 44.2% in mainland China, with an estimated 589 million people infected.<sup>10</sup> 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.<sup>11</sup> The recurrence rate of *H. pylori* increases with time after eradication and varies by region, gender and eradication methods.<sup>11</sup> 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.<sup>12</sup> Polyphenols may contribute to gastrointestinal health, as these bioactive compounds can inhibit *H. pylori* proliferation.<sup>13</sup> Several studies indicate that these polyphenol compounds positively affect *H. pylori* eradication.<sup>14–21</sup> However, several experimental and clinical studies have shown different results.<sup>22,23</sup> 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<sup>24</sup> 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

### 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 macrocarpon) 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
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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.

### 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 H<sub>2</sub>-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.<sup>25</sup> 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  $\chi^2$  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  $I^2 > 50\%$ .<sup>26</sup> Subgroup analyses were conducted based on different treatment schemes and polyphenol compound species.

### Patient and public involvement

No patient was involved.

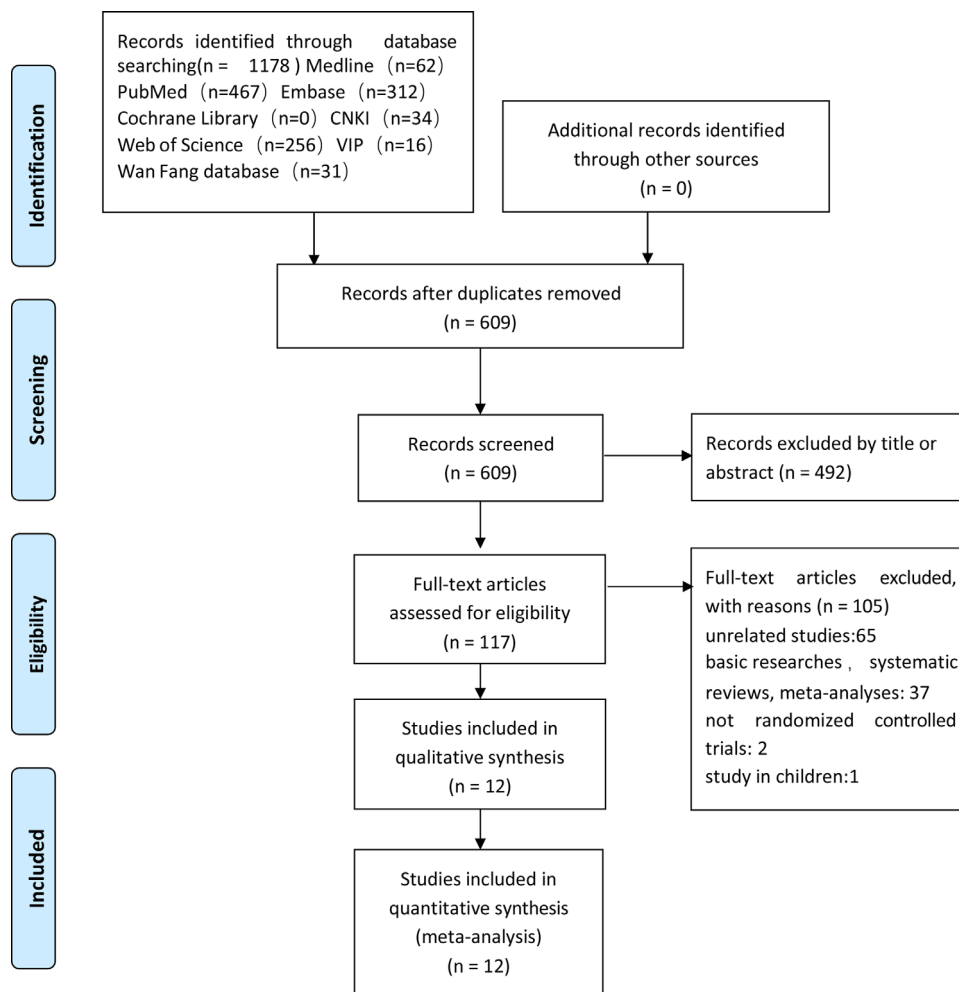
## RESULTS

### 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<sup>27–34</sup> were conducted in Iran, two<sup>18 35</sup> in China, and the remaining studies were conducted in Israel<sup>36</sup> and India,<sup>37</sup> respectively. These studies were published between 2005 and 2021. All the studies were RCTs. Of the 12 studies, two studies<sup>27 28</sup> evaluated the efficacy of curcumin in eradicating *H. pylori*, four studies<sup>18 29 35 36</sup> evaluated the efficacy of cranberry, four studies<sup>30–32 37</sup> assessed the efficacy of liquorice, one study<sup>34</sup> evaluated the efficacy of garlic, and one study<sup>33</sup> 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 <i>et al</i> <sup>27</sup>            | Unclear risk               | Unclear risk           | Unclear risk                           | Unclear risk                   | Low risk                | Low risk            | Unclear risk |
| Khonche <i>et al</i> <sup>28</sup>           | Unclear risk               | Unclear risk           | Low risk                               | Low risk                       | Low risk                | Low risk            | Unclear risk |
| Shmuely <i>et al</i> <sup>36</sup>           | Unclear risk               | Unclear risk           | Low risk                               | Low risk                       | Low risk                | Low risk            | Unclear risk |
| Zhang <i>et al</i> <sup>18</sup>             | Unclear risk               | Unclear risk           | Low risk                               | Low risk                       | Low risk                | Low risk            | Unclear risk |
| Li <i>et al</i> <sup>35</sup>                | Low risk                   | Unclear risk           | Low risk                               | Low risk                       | Low risk                | Low risk            | Unclear risk |
| Seyyedmajidi <i>et al</i> <sup>29</sup>      | Unclear risk               | Unclear risk           | Unclear risk                           | Unclear risk                   | Low risk                | Low risk            | Unclear risk |
| Puram <i>et al</i> <sup>37</sup>             | Low risk                   | Unclear risk           | Low risk                               | Low risk                       | Low risk                | Low risk            | Unclear risk |
| Hajiaghamohammadi <i>et al</i> <sup>30</sup> | Unclear risk               | Unclear risk           | Unclear risk                           | Unclear risk                   | Low risk                | Low risk            | Unclear risk |
| Rahnama <i>et al</i> <sup>31</sup>           | Unclear risk               | Unclear risk           | Low risk                               | Low risk                       | Low risk                | Low risk            | Unclear risk |
| Momeni <i>et al</i> <sup>32</sup>            | Unclear risk               | Unclear risk           | Low risk                               | Low risk                       | Low risk                | Low risk            | Unclear risk |
| Mirmiran <i>et al</i> <sup>33</sup>          | Low risk                   | Low risk               | Unclear risk                           | Unclear risk                   | Low risk                | Low risk            | Unclear risk |
| Hekmatdoost <i>et al</i> <sup>34</sup>       | 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.<sup>25</sup> The methodological quality of the included trials was generally poor. In random sequence generation, three trials<sup>33 35 37</sup> 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<sup>18 27–32 34 36</sup> did not clearly describe the randomisation procedure. Methods for double-blind were described by seven of the studies.<sup>18 28 31 32 35–37</sup> One study<sup>33</sup> 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<sup>18 35 37</sup> compared the effects of polyphenols with placebo on the eradication rate of *H. pylori* infection; six studies<sup>27–30 33 36</sup> compared the effects of polyphenols along with triple

therapy on the eradication rate of *H. pylori* infection; two studies<sup>31 32</sup> compared the effects of polyphenol plus triple therapy with bismuth triple therapy; one study<sup>34</sup> 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<sup>28 32 37</sup> provided information regarding side effects. During one study,<sup>32</sup> no

**Table 2** The characteristics of each included study

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

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.

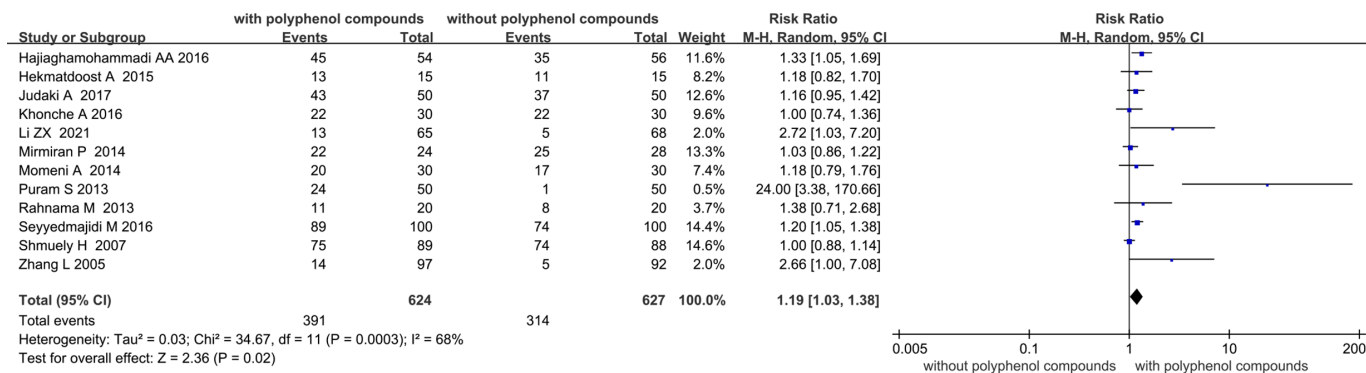
side effects or interactions (such as severe hypertension, muscular weakness or diarrhoea) were reported that led to treatment discontinuation. The side effect rates were observed in two RCTs,<sup>28 37</sup> including 160 patients. The most frequent adverse reactions were diarrhoea, headache and vomiting, 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.<sup>27 28</sup> The cranberry therapy subgroup included four studies.<sup>18 29 35 36</sup> The liquorice therapy subgroup included four studies,<sup>30–32 37</sup> while one study<sup>34</sup> was enrolled as the garlic therapy subgroup and one<sup>33</sup> 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.

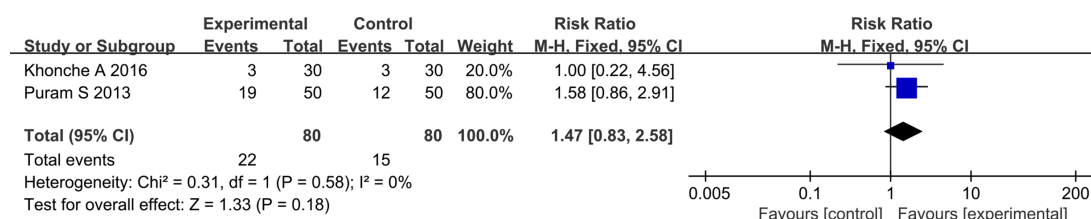
#### Publication bias

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.

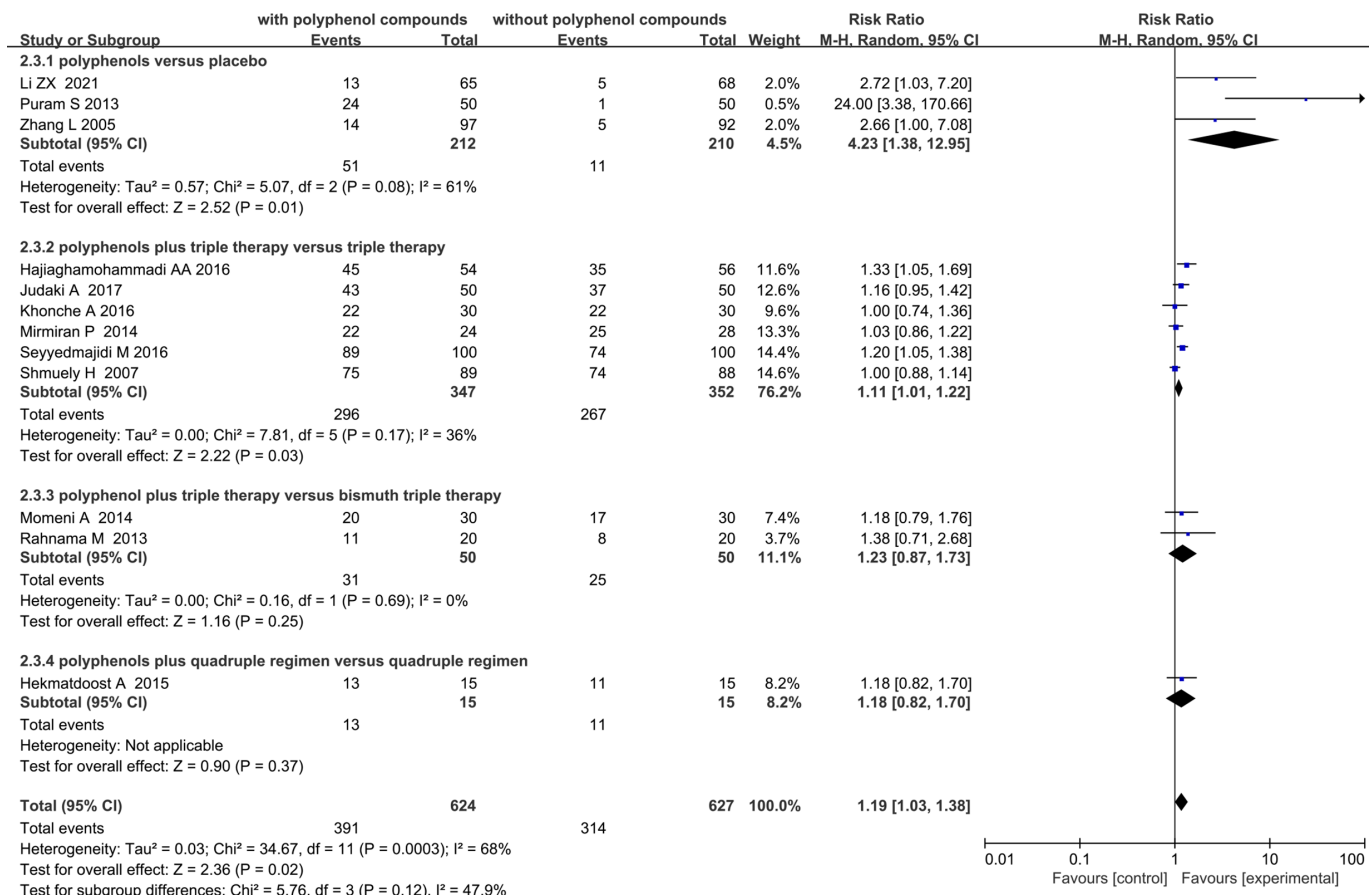
## DISCUSSION

### 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<sup>18 35 37</sup> 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<sup>27–30 33 36</sup> 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.<sup>38</sup> It has also been linked with several extra-digestive diseases such as atherosclerosis,<sup>39</sup> coronary heart disease,<sup>40</sup> iron deficiency anaemia,<sup>41</sup> idiopathic thrombocytopenic purpura,<sup>42</sup> vitamin B12 deficiency,<sup>43</sup> non-alcoholic fatty liver disease,<sup>44</sup> metabolic syndrome,<sup>45</sup> diabetes mellitus,<sup>46</sup> cerebrovascular disease,<sup>47</sup> Alzheimer's disease,<sup>48</sup> Parkinson's disease,<sup>49</sup> childhood asthma,<sup>50</sup> chronic obstructive pulmonary disease,<sup>51</sup> chronic urticaria,<sup>52</sup> rosacea<sup>53</sup> and osteoporosis.<sup>54</sup> *H. pylori* eradication is required for managing *H. pylori*-related complications.

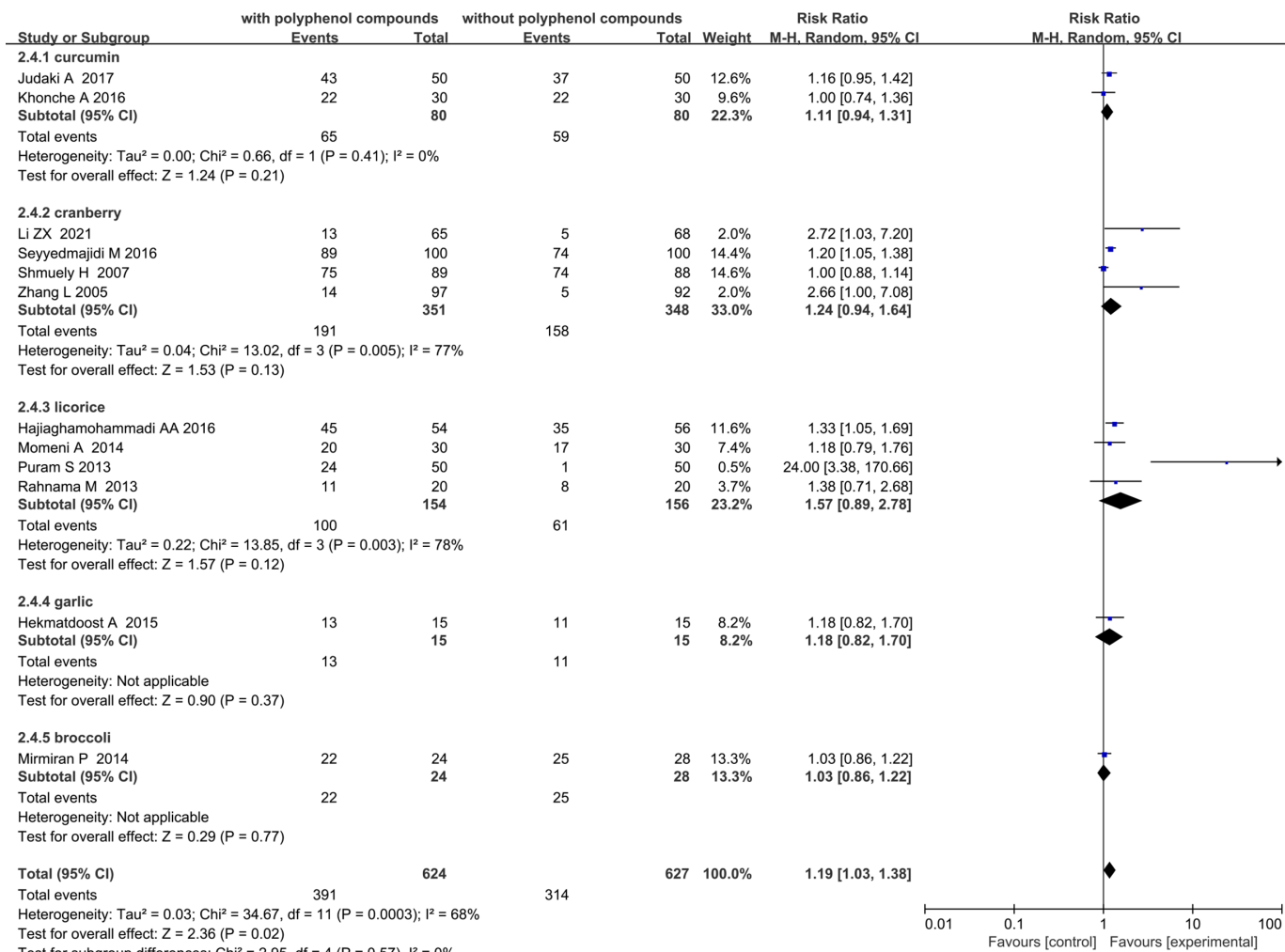
The efficacy of standard 1-week triple therapy containing clarithromycin and either metronidazole or amoxicillin combined with a PPI has decreased dramatically, with

eradication rates as low as 50%–70%.<sup>55</sup> Antibiotic resistance and patient compliance are the major causes of this decline.<sup>56</sup> Bismuth-containing quadruple therapy is now recommended as the main empirical therapy in regions with high clarithromycin and metronidazole resistance (>15%).<sup>57</sup> Concomitant, sequential and hybrid therapies are also recommended for treating *H. pylori* infection.<sup>58</sup> However, there are currently few, if any, regimens consistently achieve eradication rates exceeding 90%.<sup>59</sup>

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.

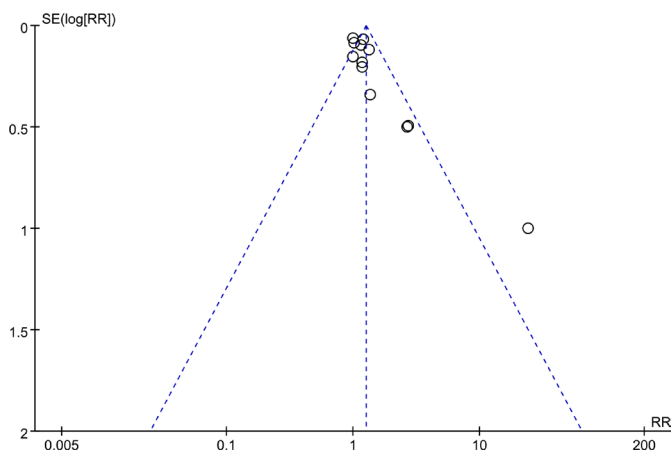
#### Other studies supporting the findings

Polyphenols possess numerous pharmacological and therapeutic properties, including antioxidant and anti-inflammatory activities.<sup>60</sup> 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.<sup>60</sup> The yellow pigment curcumin (diferuloylmethane) is a key poly-phenolic molecule found in turmeric root.<sup>61</sup>



**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.<sup>62</sup> Its effects on *H. pylori* infection have been repeatedly confirmed in animal and human models.<sup>14–17</sup> It has been demonstrated in animal experiments that curcumin treatment exhibited a significant anti-inflammatory effect in *H. pylori*-infected gastric mucosa.<sup>63</sup> 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.<sup>36</sup> Mechanisms of cranberry’s suppression of *H. pylori* may be due to phenolic compounds found in the fruit.<sup>35</sup> In a clinical trial conducted on colonised Chinese adults, cranberry juice eradicated *H. pylori* in 14.4% of subjects.<sup>18</sup> 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.<sup>64</sup> 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*.<sup>19</sup>

Several studies have shown that extracts from raw garlic or garlic powder tablets maintain in vitro activity against *H. pylori*.<sup>65,66</sup> Moreover, licorice (liquorice or sweet wood) has been shown to have anti-*H. pylori* effects.<sup>20</sup> 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.<sup>67</sup> Another study showed that an aqueous extract of glycyrrhiza glabra significantly inhibited *H. pylori* adhesion to human stomach tissue.<sup>68</sup> 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.<sup>21</sup> 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.<sup>69</sup>

### 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*.<sup>27, 28</sup> 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.<sup>18, 35</sup> 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.<sup>29</sup> 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*.<sup>37</sup> Furthermore, liquorice (380mg, two times per day, 2 weeks) is commonly added to triple or quadruple schemes.<sup>30–32</sup> This meta-analysis included one study on garlic, which did not support a role for garlic in the treatment of *H. pylori* infection.<sup>34</sup> 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, 4 weeks) plus standard triple therapy affect *H. pylori* eradication.<sup>33</sup>

### 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.

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