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META-ANALYSIS

Allicin as add-on therapy for *Helicobacter pylori* infection: A systematic review and meta-analysis

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Author contributions: Si XB, Lan Y, and Zhang S performed study design; Si XB and Zhang S performed study selection; Si XB and Wang S performed data collection; Si XB, Zhang XM, and Huo LY performed data analysis; Si XB performed manuscript drafting; Lan Y performed critical review of the manuscript. All authors revised the manuscript and approved the final version.

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Abstract

BACKGROUND

Allicin (2-propene-1-sulfinothioic acid S-2-propenyl ester, diallyl thiosulfinate) extracted from garlic, has proven activity against *Helicobacter pylori* (*H. Pylori*) infection. In recent years, clinical trials have explored its utility as an add-on therapy with variable outcomes reported.

AIM

To perform a systemic review of allicin as an add-on treatment for *H. Pylori* infection and assess its efficacy in randomized controlled trials (RCTs).

METHODS

Electronic databases including MEDLINE, EMBASE, the Web of Science, the Cochrane Database, the China National Knowledge Infrastructure Database, Chinese VIP Information Databases, Chinese Medical Databases, and the Wan-Fang Database were searched for keywords including "allicin", "*Helicobacter pylori*", "randomized clinical trials", and their synonyms. A meta-analysis was performed using the fixed-effects model for low heterogeneity and the random-effects model for high heterogeneity with sensitivity analysis. Bias was evaluated using Egger's tests. Trial sequential analysis (TSA) was used to evaluate information size and treatment benefits. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the level of quality, and studies were classed as "high quality", "moderate quality", "low quality", and "very low quality".

RESULTS

A total of eight RCTs consisting of 867 participants (435 from the allicin group and 432 from the control group) were included. Eradication rate in the allicin

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group (93.33%, 406/435) was significantly higher than that of the control group (83.56%, 361/432) [I^2 = 0%, odds ratio (OR) = 2.75, 95% confidence interval (CI): 1.74-4.35, P < 0.001]. The healing rate of ulcers following *H. pylori* therapy in the allicin group (86.17%, 349/405) was significantly higher than that of the control group (75.87%, 305/402) [I^2 = 0%, OR = 2.05, 95%CI: 1.39-3.03, P < 0.001]. The total remission rate of peptic ulcers across all allicin groups was 95.99%, which was significantly higher than that of controls [95.99% (359/374) *vs* 89.25% (332/372), I^2 = 0, heterogeneity P = 0.84, OR = 3.13, 95%CI: 1.51-6.51, P =0.002]. No significant differences in side effects were observed. TSA suggested that the trials were of sufficient standard to draw reliable conclusions. The quality of outcomes including eradication rates and side effects was graded as "very low" due to downgrades for "risk of bias" and "indirectness". Other outcomes such as ulcer healing rates and total ulcer remission rates were graded as "low" due to downgrades for "risk of bias".

CONCLUSION
Allicin as an add-on therapy improves *H. pylori* eradication, healing of ulcers, and remission of symptoms. These results are suggested to be treated with caution due to limited quality.

Key words: Allicin; *Helicobacter pylori*; Randomized controlled trials; Add-on therapy; Systematic review; Meta-analysis

Core tip: The present systematic review assessed the efficacy and safety of allicin as an add-on treatment to PPI triple therapy and bismuth containing quadruple therapy for *Helicobacter pylori* infection. As a result, allicin was confirmed to increase the eradication rate, healing rate of ulcers, and remission rate of digestive symptoms but not rate of side effects.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a Gram-negative microaerophilic bacterium that colonizes the gastric mucosa[1]. Globally, ≥ 50% of individuals are infected, and the prevalence is higher in developing countries[2]. *H. pylori* is a major cause of gastritis and peptic ulcers, as well as atrophy, intestinal metaplasia, intraepithelial neoplasia, and mucosa-associated lymphoid tissue lymphoma (MALT)[1,2].

Proton pump inhibitors (PPIs) in combination with antibiotics have been used to treat *H. pylori* infection. PPI triple therapy (PTT), consisting of PPI and two antibiotics such as amoxicillin and clarithromycin, is the recommended front-line treatment[2] but its eradication rates have decreased to ~70% or lower[2]. Antibiotic resistance, particularly towards clarithromycin and metronidazole, is the major cause of this decline[3]. Bismuth containing quadruple therapy (BCQT) is now recommended as the main empirical therapy in regions with high clarithromycin and metronidazole resistance (> 15%)[1]. However, eradication rates using BCQT range from 70% to 94%, questioning its effectiveness as a therapeutic strategy[1,2,4]. Therefore, new strategies to treat *H. pylori* infection are needed.

Choosing new alternatives with high efficiency and less side effects is one of the possible desirable options in the treatment of *H. pylori* infection[5]. In recent years, a series of studies were performed to explore the anti-*H. pylori* activities and clinical application of various agents as alternative therapies, such as plants[6,7], probiotics[8], and gastric mucin[9]. However, most of them were done *in vitro*[5]. *In vivo* studies as well as clinical trials are needed.

Garlic (*Allium sativum L.*) is one of the most widely grown vegetable crops in Asia,

and is a known medical plant worldwide. Garlic contains 33 sulfur compounds including allicin, alliin, ajoene, diallyl trisulfide (DATS) and others[10]. Previous *in vitro* studies have shown that garlic inhibits bacterial growth and colonization including *H. pylori*[11]. Several clinical trials using garlic oil and fresh oral garlic failed to show improvements in *H. pylori* infection[12,13].

Allicin (2-propene-1-sulfinothioic acid S-2-propenyl ester, diallyl thiosulfinate) is an active anti-*H. pylori* component of garlic[11]. Due to developments in pharmaceutical technology, commercial allicin tablets are available. Allicin in addition to PTT and BCQT has been trialed as an anti-*H. pylori* therapy, with variable results[14-23]. Based on these studies, we performed this meta-analysis to systemically review the efficacy and safety of allicin as an add-on therapy to PTT/BCQT for *H. pylori* infection.

MATERIALS AND METHODS

Protocol

Preplanned protocols were established with protocols.io (https:// www.protocols.io) under the title "Allicin as a Complementary Medicine of Triple/Quadruple Therapy for *Helicobacter pylori*; A Systemic review and Meta-analysis of Randomized Controlled Trials (protocol)". (https://dx.doi.org/10.17504/protocols.io.4ybgxsn)

Information sources and search strategy

We performed a systemic literature search in MEDLINE, EMBASE, the Web of Science, the Cochrane Database, the China National Knowledge Infrastructure Database, Chinese VIP Information Databases, Chinese Medical Databases, and the Wan-Fang Database from inception to June 1, 2019. Academic journals, dissertations, and conference proceedings were included irrespective of gray literature status. The search terms included "*Helicobacter pylori*", "allicin", "randomized clinical trials", and their synonyms. The search strategy is listed in Appendix 1, with PubMed as an example. Reference lists were searched for potentially relevant titles. Literature searches and analysis were preplanned prior to the systemic review.

Inclusion and exclusion criteria

The following criteria were used for literature selection: (1) The subjects enrolled were adults with *H. pylori* infection with/without *H. pylori*-related disease including gastritis and ulcers. The diagnosis of *H. pylori* infection was based on positive histology, rapid urease tests (RUT), or urease breath tests (UBT); (2) Subjects in the treatment group underwent interventions using allicin plus PTT or BCQT. The control group received PTT/BCQT alone; (3) PTT/BCQT regimens in both groups were identified; (4) The main outcome was the eradication rate. Secondary outcomes were side effects, the relief of digestive symptoms, and ulcer healing (healing rate and total effectiveness rate); and (5) The study design consisted of randomized controlled trials (RCTs).

Studies that met the following criteria were excluded: (1) Duplicate articles or evaluation of the same samples; (2) Articles published as reviews, meta-analysis, or protocols; (8) Studies recruiting children; and (9) *In vitro* studies.

Study selection and data collection

All retrieved trials were independently screened by two reviewers (Xiao-Bei Si and Shuo Zhang). Titles and abstracts were screened for all relevant articles. Full texts were screened for further assessments according to the inclusion and exclusion criteria. Disagreements were resolved by discussion or through consultation with a second specialist.

Two reviewers (Xiao-Bei Si and Shuai Wang) independently extracted data from the included RCTs. Authors, publication year, sample size, interventions, eradication rate, and secondary outcomes (remission of digestive symptoms, healing rate of peptic ulcers, and side effects) were included. Eradication rate was defined as *H. pylori* negativity following eradication therapy[1]. Peptic ulcers were classed as healed, effective, or ineffective following endoscopic examination before and after eradication therapy. The healing of peptic ulcers was defined as the disappearance of ulcer lesions and surrounding inflammation. Effectiveness was defined as a reduction in ulcer lesions to ≤ 50% of the original size, whilst non-effectiveness was deemed as ≥ 50% of the lesion remaining. Healing rate was defined as the number of cured cases divided by the total number of cases. Total effectiveness rate was defined as the percentage of patients whose peptic ulcers were classed as healing and/or effectiveness [Total effectiveness rate = (total number – non-effectiveness number)/total number × 100%][24]. The remission of abdominal pain was defined as a disappearance of abdominal pain after treatment. Disappearing abdominal pain was defined as the

time from the initiation of *H. pylori* treatment to the disappearance of abdominal pain. Side effect rate was defined as the percentage of patients with at least one side effect[24].

Risk of bias assessment

We evaluated the risk of bias of the included articles using the Cochrane handbook[25]. Methodological quality was assessed with regard to random sequence generation, allocation concealment, the blinding of participants and personnel, the blinding of outcome assessments, incomplete outcome data, selective reporting, and other bias. Risks of bias were categorized as "low", "high", or "unclear".

Statistical analysis

Meta-analysis was performed using Comprehensive Meta-analysis software (version 2.2.064; Biostat Inc, Englewood, United States). Sensitivity analysis was performed depending on the heterogeneity across the included studies. Statistical heterogeneity was assessed by I^2 statistics. The Chi-square test $P < 0.10$ or I^2 values ≥ 50% indicated heterogeneity. Trials showing either clinical heterogeneity or statistical heterogeneity were combined according to the random-effects model. The fixed-effects model was otherwise used. Publication bias was analyzed using an Egger's test. Funnel plots were performed if >10 studies were included.

Trial sequential analysis (TSA)

TSA was used to evaluate treatment benefits based on the sample sizes using TSA software (version 0.9.5.10 Beta; Copenhagen Trial Unit, Copenhagen, Denmark) with $\alpha = 5\%$ and $1\text{-}\beta = 80\%$. The anticipated relative risk reduction was based on the pooled estimate of available trials. Boundaries were monitored to confirm the early termination of the trials when *P*-values were sufficiently small enough to confirm the anticipated effects. The chance of random errors increased due to insufficient comparisons and the repetitive testing of pooled data. When cumulative *Z*-curves crossed sequential monitoring boundaries, a sufficient level of evidence is obtained for the intervention. When *Z*-curves did not cross the boundaries, the conclusions for the intervention were not justified[26].

Evidence quality evaluation

The quality of the meta-analysis was evaluated using The Grading of Recommendations Assessment, Development and Evaluation (GRADE). As per GRADE criteria, certainty was rated as downwards to include risk of bias, inconsistency, indirectness, imprecision, and publication bias. Certainty was increased through large effects, dose-response relationships, and the adjustment of all plausible residual confounding effects. Evidence was summarized into four categories: "High quality", "moderate quality", "low quality", and "very low quality"[27].

RESUTLS

Literature analysis and quality assessment

We identified 211 records using our established search strategy. Of these, 82 were excluded as duplicated records, 114 were non-clinical trials, 14 were unrelated articles, and one trial was excluded due to allicin plus non-PTT/BCQT regimens. In total, 10 clinical trials were retrieved for further full text screening. One trial[14] was excluded as the participants underwent non-standard triple therapy of amoxicillin-bismuth-PPI. A single trial[23] was excluded as the triple therapies in the allicin and control groups differed. Thus, a total of eight RCTs with 867 participants (435 from the allicin group and 432 from the control group) were finally included. The sample population of each RCT ranged from 60 to 220. A flow chart of article screening and selection processes is shown in Figure 1. One study was performed in Turkey whilst the rest were performed in China. The characteristics of each included study are summarized in Table 1.

We used the Cochrane handbook tool to assess the quality of the included studies. No studies reported methods of randomization or concealment, despite claims of "randomized trials". No studies implemented blindness, and one study[22] reported incomplete outcome data. No studies reported the existence of reporting bias. Table 2 shows the results of quality assessments. No included studies registered published protocols. An Egger's test showed no publication bias (Intercept: -1.21506, $P = 0.25$). Funnel plots were not performed due to the insufficient study number ($n < 10$).

Eradication rates

We compared the eradication rates of *H. pylori* between allicin and control groups.

Table 1 Summary of included studies

Ref.	N	Participants	Diagnostic methods	Allicin group	Control group	Therapy duration	Therapies after eradication	Outcomes
Zhan *et al*, 2013[15]	60	Hp-infected patients with peptic ulcer	i OR ii i Hp histology; ii ^{14}C-UBT or RUT in latest 7 days before endoscopy test	Am: 1000 mg b.i.d. F: 100 mg b.i.d E: 40 mg q.d. Al: 40 mg t.i.d.	Am: 1000 mg b.i.d. F: 100 mg b.i.d E: 40 mg q.d.	7 d	E: 40 mg q.d. for another 3 weeks in both groups	*a, b, c, d*
Bai *et al*, 2008[16]	198	Hp-infected patients with peptic ulcer	i AND ii i Histology or RUT; ii ^{14}C-UBT	Am: 1000 mg b.i.d. M: 400 mg b.i.d O: 20 mg b.i.d. Al: 40 mg t.i.d.	A: 1000 mg b.i.d. M: 400 mg b.i.d O: 20 mg b.i.d.	7 d	O: 20 mg b.i.d. for another 3 weeks in both groups	*a, b, c*
Wang *et al*, 2006[17]	61	Hp-infected patients with peptic ulcer	i AND ii i Hp histology or RUT; ii ^{14}C-UBT	F: 100 mg b.i.d C: 250 mg b.i.d O: 20 mg b.i.d. Al: 40 mg t.i.d.	F: 100 mg b.i.d C: 250 mg b.i.d O: 20 mg b.i.d.	7 d	O: 20 mg b.i.d. for another 3 weeks in both groups	*a, b, d*
Li *et al*, 2014[18]	86	Hp-infected patients with peptic ulcer	^{14}C-UBT	Am: 1000 mg b.i.d. F: 100 mg b.i.d E: 40 mg q.d. Al: 40 mg t.i.d.	Am: 1000 mg b.i.d. F: 100mg b.i.d E: 40 mg q.d.	7 d	E: 40 mg q.d. for another 4 weeks in both groups	*a, b, c, d*
Kochar *et al*, 2001[19]	60	Hp-infected patients with peptic ulcer	Hp histology	Am: 1000 mg b.i.d. C: 500 mg b.i.d La: 10 mg b.i.d. Al: 1.2 mg q.d.	Am: 1000 mg b.i.d. C: 500 mg b.i.d La: 10 mg b.i.d.	14 d	None	*a, d*
Guan *et al*, 2017[20]	90	Hp-infected patients with peptic ulcer	^{14}C-UBT	Am: 1000 mg b.i.d. F: 100 mg b.i.d E: 40 mg q.d. Al: 40 mg t.i.d.	Am: 1000 mg b.i.d. F: 100 mg b.i.d E: 40 mg q.d.	7 d	E: 40 mg q.d. for another 3 weeks in both groups	*a, b, c, d*
Zhao *et al*, 2015[21]	92	Hp-infected patients with peptic ulcer	^{14}C-UBT	T: 500 mg b.i.d. C: 500 mg b.i.d I: 5 mg b.i.d. B: 220 mg t.i.d. Al: 40 mg t.i.d.	T: 500 mg b.i.d. C: 500 mg b.i.d I: 5 mg b.i.d. B: 220 mg t.i.d.	7 d	I: 5 mg b.i.d. for another 3 weeks in both groups	*a, b, d, e*
Chen *et al*, 2016[22]	220	Hp-infected patients with peptic ulcer	^{14}C-UBT	T: 500 mg b.i.d. C: 500 mg b.i.d I: 5 mg b.i.d. B: 220 mg t.i.d. Al: 40 mg t.i.d.	T: 500 mg b.i.d. C: 500 mg b.i.d I: 5 mg b.i.d. B: 220 mg t.i.d.	7 d	Al: 40 mg t.i.d. and I: 5 mg b.i.d. for another 3 weeks in both groups	*a, b, c, e*

N: Number of participants; Hp: *Helicobacter pylori*; Am: Amoxicillin; F: Furazolidone; E: Esomeprazole; C: Clarithromycin; T: Tinidazole; O: Omeprazole; La: Lansoprazole; Le: Levofloxacin; I: Ilaprazole; R: Rabeprazole; B: Bismuth potassium citrate tablets; Al: Allicin; RUT: Rapid urease test; ^{14}C-UBT: ^{14}C-urea breath test; q.d.: Once daily; b.i.d.: Twice daily; t.i.d.: Thrice daily; *a*: Eradication rate; *b*: Healing rate of peptic ulcers; *c*: Total remission rate of peptic ulcers; *d*: Side effect rates; *e*: Disappearance time of abdominal pain.

The eradication rates of the allicin group (93.33%, 406/435) were significantly higher than those of the control group (83.56%, 361/432) for intent-to-treat (ITT) analysis [I^2 = 0%, heterogeneity P = 0.993, odds ratio (OR) = 2.75, 95% confidence interval (CI): 1.74-4.35, P < 0.001] (Figure 2) and per-protocol (PP) analysis [93.55% (406/434) *vs* 83.76% (361/431), I^2 = 0%, heterogeneity P = 0.996, OR = 2.81, 95%CI: 1.77-4.47, P < 0.001][15-22].

Six studies[15-20] compared allicin plus PTT *vs* PTT alone. The eradication rates of the allicin group were significantly higher than those of the control group for both ITT analysis [92.47% (258/279) *vs* 82.61% (228/276), I^2 = 0%, OR = 2.87, 95%CI: 1.65-4.99, P < 0.001] and PP analysis [92.81% (258/278) *vs* 82.91% (228/275), I^2 = 0%, OR = 2.66, 95%CI: 1.53-4.64, P = 0.001]. A further two studies[21,22] compared allicin combined with PPI-bismuth-tinidazole-clarithromycin therapy *vs* PPI-bismuth-tinidazole-clarithromycin therapy. The eradication rates in the allicin and control groups were 94.87% (148/156) and 85.25% (133/156), respectively, which significantly differed for ITT/PP analyses [I^2 = 0%, OR = 3.19, 95%CI: 1.38-7.38, P = 0.007]. Three studies[15,18,20] compared 7-day PPI-amoxicillin-furazolidone therapy with or without allicin and reported eradication rates of 92.46% (135/146) and 81.33% (122/150), respectively, for

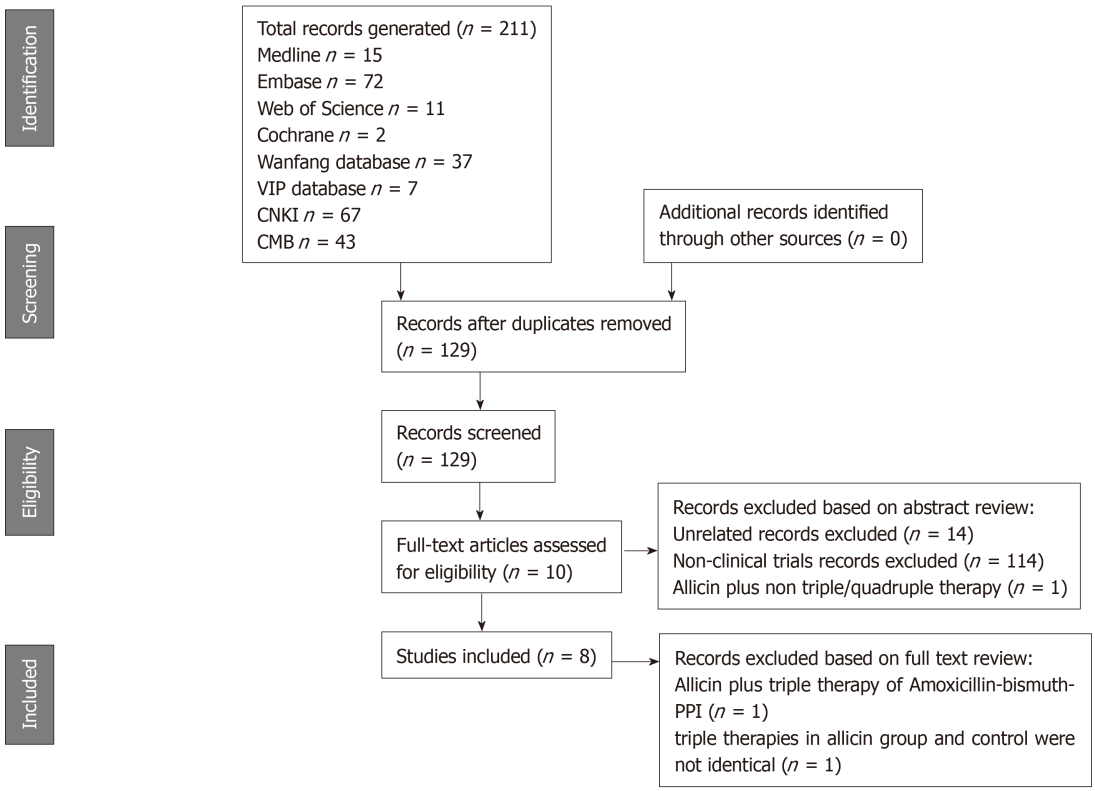

Figure 1 Flowchart showing the process of study selection for the systematic review. We identified 211 records. Totally 201 records were excluded as duplicated records, non-clinical trials, unrelated articles, and non-PTT/BCQT controlled trail. Another two records were excluded after full-text screening due to non-standard triple therapy of amoxicillin-bismuth-PPI and different triple therapy regimens in the allicin and control groups, respectively. Finally, a total of eight RCTs with 867 subjects were included. CNKI: the China National Knowledge Infrastructure Database; CMB: Chinese Medical Databases.

ITT/PP analyses [I^2 = 0%, OR = 2.38, 95%CI: 0.99-5.71, P = 0.053] (Table 3).

Healing rates of peptic ulcers

Patients with *H. pylori* related peptic ulcers across seven studies were included. The healing rates of ulcers after *H. pylori* eradication therapy in the allicin group were significantly higher those of the control group for ITT analysis [86.17% (349/405) *vs* 75.87% (305/402), I^2 = 0%, heterogeneity P = 0.536, OR = 2.05, 95%CI: 1.39-3.03, P < 0.001] (Figure 3) and PP analysis [86.39% (349/404) *vs* 76.06% (305/401), I^2 = 0%, heterogeneity P = 0.527, OR = 2.06, 95%CI: 1.40-3.05, P < 0.001][15-18,20-22].

Five studies [15-18,20] compared the healing rates following 7 days of allicin combined with PTT *vs* PTT alone. The allicin group showed significantly higher rates of healing rates compared to the control group for both ITT analysis [80.32% (200/249) *vs* 68.29% (168/246), I^2 = 0%, OR = 2.14, 95%CI: 1.39-3.29, P = 0.001] and PP analysis [80.65% (200/248) *vs* 68.57% (168/245), I^2 = 0%, OR = 1.93, 95%CI: 1.25-2.96, P = 0.003]. Upon comparison of allicin-PPI-bismuth-tinidazole-clarithromycin *vs* PPI-bismuth-tinidazole-clarithromycin, significantly higher healing rates in the allicin group were observed for ITT/PP analyses [95.51% (149/156) *vs* 87.82% (137/156), I^2 = 22.924, OR = 2.83, 95%CI: 1.13-7.10, P = 0.026][21,22]. Allicin plus PPI-amoxicillin-furazolidone showed significantly higher healing rates than the control group for ITT/PP analyses [83.62% (97/116) *vs* 65.00% (78/120), I^2 = 0%, OR = 1.90, 95%CI: 1.18-3.06][15,18,20] (Table 4).

Total remission rates of peptic ulcers

Six studies[15,16,18,20-22] reported peptic ulcer remission rates. The total remission across allicin groups was significantly higher than that of controls for ITT/PP analyses [95.99% (359/374) *vs* 89.25% (332/372), I^2 = 0, heterogeneity P = 0.84, OR = 3.13, 95%CI: 1.51-6.51, P = 0.002] (Figure 4).

Four studies[15,16,18,20] compared allicin combined with PTT *vs* PTT alone for total remission rates for ITT/PP analyses [93.12% (203/218) *vs* 81.48% (176/216), I^2 = 0, OR = 3.13, 95%CI: 1.51-6.51, P = 0.004]. Studies comparing BCQT plus allicin *vs* BCQT alone reported total remission rates of 100%[21,22]. Allicin plus PPI-amoxicillin-

Table 2 Results of quality assessment

Ref.	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Zhan, 2013[15]	Unclear	Unclear	High risk of bias	Unclear	Low risk of bias	Unclear	Unclear
Bai, 2008[16]	Unclear	Unclear	High risk of bias	Unclear	Low risk of bias	Unclear	Unclear
Wang, 2006[17]	Unclear	Unclear	High risk of bias	Unclear	Low risk of bias	Unclear	Unclear
Li, 2014[18]	Unclear	Unclear	High risk of bias	Unclear	Low risk of bias	Unclear	Unclear
Kochar, 2001[19]	Unclear	Unclear	High risk of bias	Unclear	Low risk of bias	Unclear	Unclear
Guan, 2017[20]	Unclear	Unclear	High risk of bias	Unclear	Low risk of bias	Unclear	Unclear
Zhao, 2015[21]	Unclear	Unclear	High risk of bias	Unclear	Low risk of bias	Unclear	Unclear
Chen, 2016[22]	Unclear	Unclear	High risk of bias	Unclear	High risk of bias	Unclear	Unclear

furazolidone showed higher total remission rates of 93.97% compared to 7-day PPI-amoxicillin-furazolidone therapy for ITT/PP analyses [93.97% (109/116) *vs* 80.83% (97/120), I^2 = 0%, OR = 4.87, 95%CI: 1.36-17.50, P = 0.015][15,18,20] (Table 5).

Side effects

Six studies[17-22] reported side effects in the allicin group and control group without statistical significance for ITT analysis [5.90% (18/305) *vs* 9.53% (29/304), I^2 = 0%, heterogeneity P = 0.591, OR = 0.61, 95%CI: 0.32-1.16, P = 0.133] (Figure 5) and PP analysis [5.92% (18/304) *vs* 9.57% (29/303), I^2 = 0%, heterogeneity P = 0.593, OR = 0.61, 95%CI: 0.32-1.16, P = 0.132].

Four studies[17-20] compared allicin combined with PTT *vs* PTT alone for side effects. No significant differences were observed for ITT analysis [7.38% (11/149) *vs* 13.51% (20/148), OR = 0.52, 95%CI: 0.22-1.20, P = 0.125] and PP analysis [5.92% (18/304) *vs* 9.57% (29/303), OR = 0.61, 95%CI: 0.32-1.16, P = 0.132]. Two studies[18,20] compared allicin-PPI-amoxicillin-furazolidone therapy *vs* PPI-amoxicillin-furazolidone alone, which showed no significant differences between groups for ITT/PP analyses [2.27% (2/88) *vs* 7.95% (7/88), I^2 = 0%, OR = 0.27, 95%CI: 0.054-1.34, P = 0.110]. No significant differences were observed for allicin-PPI-bismuth-tinidazole-clarithromycin *vs* PPI-bismuth-tinidazole-clarithromycin alone for ITT/PP analyses [4.49% (7/156) *vs* 5.77% (9/156), I^2 = 0%, OR = 0.77, 95%CI: 0.28-2.13, P = 0.612][21,22] (Table 6).

Remission of abdominal pain

Two studies[21,22] reported the remission of abdominal pain in both groups. Chen *et al*[22] reported the subsidence of abdominal pain after 1.52 ± 0.5 d in the allicin group compared to 2.20 ± 1.2 d in control subjects. This significant difference was in contrast to that reported by Zhao *et al*[21] (average times of 1.55 ± 0.5 d and 1.80 ± 0.6 d in the allicin and control groups, respectively). A further meta-analysis showed more rapid cessation of abdominal pain in the allicin group [standard mean difference (SMD) = -0.653, 95%CI: -0.88--0.43, P < 0.001] (Figure 6).

Sensitivity analysis

From the sensitivity analysis, the individual removal of studies had no statistical significance and the pooled OR was unchanged.

TSA

TSA of the eradication rates showed that the required information size (RIS) of 295 participants were required to calculate the eradication rates of our meta-synthesis, based on the following statistical indicators of I error probability (α = 5%): Type II error probability (β = 20%); relative risk reduction (RRR = -12.41%); and incidence in the control arm (Pc = 83.56%, derived from the meta-analysis data). Cumulative Z-curve crossed the trial sequential monitoring boundary, showing significant evidence of eradication rates. The cumulative values of the Z scores crossed conventional boundary values, trial sequential monitoring boundaries, and RIS line, suggesting that the trials were sufficient, and no alterations of the conclusions were likely (Figure 7).

A further TSA of the healing rates showed that RIS of 635 participants was required to calculate the healing rates based on the following statistical indicators of I error probability (α = 5%): β = 20%; RRR = -10.49%; and Pc = 75.87%. Cumulative Z-curves crossed the trial sequential monitoring boundary, which showed sufficient evidence of statistically significant healing rates. Z-curves crossed the conventional boundary values, and trial sequential monitoring boundaries reached the RIS line, suggesting

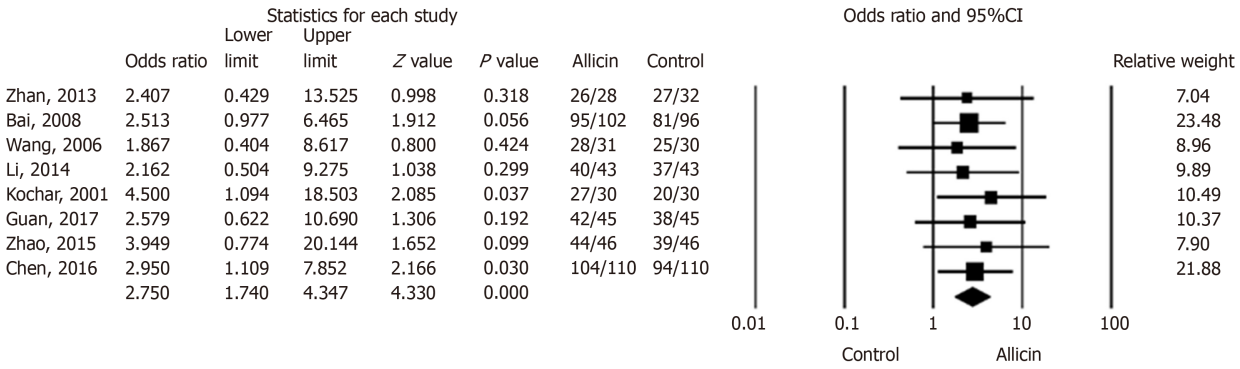

Figure 2 Eradication rates of *Helicobacter pylori* between allicin and control groups (intent-to-treat analysis). The eradication rate of the allicin group (93.33%, 406/435) was significantly higher than that of the control group (83.56%, 361/432) for intent-to-treat (ITT) analysis (Odds ratio = 2.75, 95% confidence interval: 1.74-4.35), $P < 0.001$). CI: Confidence interval.

that the trials sufficiently drew reliable conclusions (Figure 8).

Evidence quality evaluation

We downgraded by two levels for the "risk of bias" as the included studies did not state randomization methods, despite claiming to be randomized. In addition, the blinding of patients was not described in all included studies, which were therefore classed as non-blind. Studies were further downgraded due to "indirectness". We assessed the efficacy of eradication rates as primary outcomes in patients with *H. pylori* infection. However, participants of the seven included studies (7/8, 87.50%) had *H. pylori* infection combined with peptic ulcers. These differences might lead to further bias. As a result, the overall certainty of the eradication rates was "very low" due to such downgrades. The outcomes of "healing rates of peptic ulcers" and "total remission rates of peptic ulcers" were "low" due to the "risk of bias" as all included studies did not state randomization and blinding methods despite claiming to be randomized. The outcome of "side effect rates" was graded as "very low" due to similar issues. GRADE evidence profiles are shown in Table 7.

DISCUSSION

H. pylori infection is one of the pathogenic factors of gastritis, peptic ulcers, and MALT[1]. *H. pylori* eradication plays an important role in the treatment of digestive disease and reduces the lifetime risk of gastric cancer[1]. In recent years, antibiotic resistance, particularly metronidazole and clarithromycin, have threatened *H. pylori* therapy[2]. Nearly 15% of *H. pylori* isolates develop multiple drug resistance (resistance to three or more antibiotics)[3,28]. As a result, the eradication rates of PTT have decreased to 70%-85%[1,29]. Accordingly, clarithromycin-based triple therapy is not recommended in areas of high resistance[3]. Compared to PTT, BCQT is an accepted strategy to increase eradication rates[1], particularly in areas of clarithromycin and metronidazole resistance[1]. According to the meta-analysis performed by Venerito *et al*[30], the eradication rates of bismuth-based quadruple therapy range from 68.8% to 91.0% (intention-to-treat analysis) with a total eradication rate of 77.6%. Both therapies failed to effectively control *H. pylori*. Considering increased antibiotic resistance rates and treatment failure rates, new *H. pylori* treatment strategies need to be developed. Accordingly, finding alternative non-antibiotic approaches is one of new strategies for *H. pylori* treatment.

Garlic is anti-bacterial and has been used to treat infectious diseases. In 1998, Chung *et al*[31] first reported that garlic components can suppress *H. pylori* growth. Diallyl sulfide (DAS) or diallyl disulfide (DADS) was shown to elicit bactericidal effects on *H. pylori* cultures. During that period, commercial garlic preparations containing either garlic powder (GP) or garlic oil (GO) were assessed. GP is a preparation of sliced, dried, and pulverized garlic cloves to which water is added. GO is produced by heating crushed garlic cloves to 100 °C, collecting the vapor as a distillate, and diluting the final product in vegetable oil[32]. Although O'Gara *et al* demonstrated the anti-*H. pylori* effects of GO and GP *in vitro*, determined through minimal inhibitory concentrations ranging from 8 to 32 mg/mL and 250 to 500 mg/mL, respectively, subsequent clinical studies failed to confirm this activity. Aydin *et al*[12] reported a prospective cohort of 20 *H. pylori* infected individuals treated with

Table 3 Subgroup analyses of eradication rates

Comparison	Eradication rate (%)		Heterogeneity		OR	95%CI	*P* value
	Allicin group	Control	I^2 (%)	*P* value			
Allicin + PTT *vs* PTT[15-20] (ITT)	92.47	82.61	0	0.975	2.87	1.65-4.99	< 0.001
Allicin + PTT *vs* PTT[15-20] (PP)	92.81	82.91	0	0.984	2.66	1.53-4.64	0.001
Allicin-PPI-B-T-C *vs* PPI-B-T-C[21,22] (ITT/PP)	94.87	85.25	0	0.764	3.19	1.38-7.38	0.007
Allicin-PPI-Am-F *vs* PPI-Am-F[15,18,20] (ITT/PP)	92.46	81.33	0	0.986	2.38	0.99-5.71	0.053

PPI: Proton pump inhibitor; PTT: Proton pump inhibitor triple therapy; Am: Amoxicillin; F: Furazolidone; C: Clarithromycin; T: Tinidazole; B: Bismuth potassium citrate tablets; ITT: Intent-to-treat analysis; PP: Pre-protocol analysis; OR: Odds ratio; CI: Confidence interval.

GO (275 mg three times per day combined with omeprazole) in whom no significant effects on *H. pylori* eradication were observed. A non-randomized crossover trial by Graham *et al*[13] treated *H. pylori* infected individuals with fresh oral garlic, with no beneficial effects reported. In 2001, McNulty *et al*[33] performed a clinical trial with GO therapy in which the subjects received one 4 mg GO capsule with their meals four times per day for 14 d. No evidence of either *H. pylori* eradication or the improvement of symptoms was observed. These negative results failed to prove the inhibitory effects of fresh garlic and GO on *H. pylori*. These failures can, however, be rationalized. First, although the levels of allicin in commercial products are roughly equivalent to those of fresh crushed garlic, the conversion of allicin to other garlic sulfides can occur during the production process[12]. Second, it is accepted that the anti-*H. pylori* effects of garlic are dose dependent but no consensus on acceptable garlic doses exists. Whether effective doses were used in these trials remains unclear.

Allicin was first defined as an antimicrobial agent in 1944[34] and was subsequently shown to have anti-*H. pylori* effects[35], the mechanism(s) of which remain undefined[35]. *H. pylori* suppression may contribute to the anti-inflammatory effects of allicin, particularly the inhibition of IL-8 and TNF-α. *H. pylori* infection inhibits heat shock proteins (HSP) and promotes lipopolysaccharidase release[36]. In recent years, the artificial synthesis of allicin in commercial preparation (40 mg per tablet) improved allicin therapy. A series of clinical trials were performed in *H. pylori* infected individuals in whom allicin was administered as an add-on treatment to PTT/BCQT to treat *H. pylori* infection and *H. pylori*-related disease. Xue *et al*[37] performed a trial in which the eradication rate of allicin with ranitidine therapy were compared to that of ranitidine alone. Negative results were reported, suggesting that garlic products fail to eradicate *H. pylori* in the absence of antibiotics.

In this review, we analyzed trials that included allicin as an add-on treatment to PTT/BCQT for *H. pylori* infection. Allicin treated groups showed an eradication rate of ~93.33%. These results were graded as "good" (90%-95%) and highlight the benefits of allicin as an add-on treatment for *H. pylori* eradication[38]. Our meta-analysis also showed that allicin plus PTT/BCQT resulted in higher healing rates and total remission rates of peptic ulcers. Several mechanisms contribute to improved ulcer responses. First, inflammatory responses play a role in the development of peptic ulcers. Allicin inhibits the activation of NF-Kβ, which inhibits the production of TNF-α, leading to anti-inflammatory effects[39]. Second, garlic extracts have protective effects and alleviate oxidative stress in gastric tissue. Such process contributes to mucosal injury and ulcer development[40]. Third, peptic ulcers result from a disturbance of aggressive and defensive factors in the stomach. Garlic extracts may enhance NO synthesis through increasing the activity of constitutive nitric oxide synthase (cNOS) and promoting the maintenance of endothelial function[41-42].

In recent years, several options such as phytotherapy[6,7] or traditional Chinese medicine[43], probiotics[8], and nutraceutical agents[44] have been proposed as alternative treatments for *H. pylori* infection. In addition to allicin, several other add-on treatments to PTT/BCQT have been investigated as well, with clinical evidence published. Berberine, extracted from *Coptis chinensis Franch*, was used to treat *H. pylori* infection through its combination with PTT. The eradication rate of berberine plus PTT was 85.89 % according to previous meta-analysis[45]. Probiotics have been used as an add-on treatment for *H. pylori* infection. Gong *et al*[29] performed a meta-analysis to evaluate the efficacy of probiotics plus PTT with an eradication rate of 80.74% reported. A further meta-analysis evaluated the effects of probiotics plus BQCT with an eradication rate of 90.76% observed[8]. Yin *et al*[42] also performed a meta-analysis that evaluated the traditional Chinese medicine Jinghua Weikang capsules plus PTT with an eradication rate of 85.47%. These therapeutic regimens did not achieve the

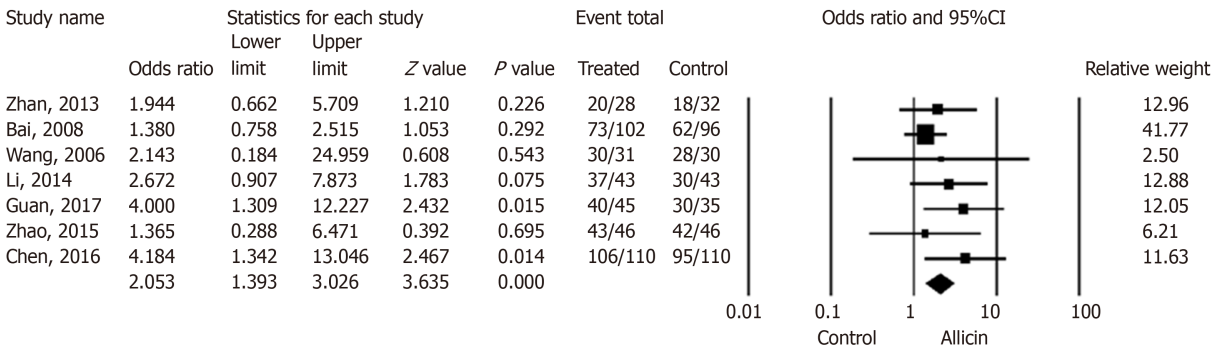

Figure 3 Healing rates of peptic ulcers between allicin and control groups (intent-to-treat analysis). The healing rate of ulcers after *H. pylori* eradication therapy in the allicin group was significantly higher that of the control group for ITT analysis (86.17% (349/405) *vs* 75.87% (305/402), odds ratio = 2.05, 95% confidence interval: 1.39-3.03, $P < 0.001$). CI: Confidence interval.

effectiveness of allicin plus PTT therapy for the treatment of *H. pylori* infection. However, the role of alternative treatment remains controversial. Previous studies mostly demonstrated that the agents as alternative treatment exhibit anti-inflammatory, immunomodulatory, and gastro-protective activities. Such activities contributed to improvement of peptic ulcer healing and remission of gastrointestinal tract symptoms. The anti-*H. pylori* activities were not well proved due to the lack of correlation between *in vitro* susceptibility and *in vivo* efficacy. What's more, no agent of alternative treatment was accepted to treat *H. pylori* infection as a monotherapy. In this regard, we speculate that anti-*H. pylori* activities of such agents, especially medical plants, exist while their active ingredients and effective dosages need to be further explored. The research and development process of allicin, *i.e.*, identification of active ingredients followed by therapeutic dosage exploration, might be a typical case of clinical application of alternative medicine.

Two previous meta-analyses[46-47] showed comparable findings, but common insufficiencies limit the quality of their evidence. Both analyses[46-47] included studies of PPI-clarithromycin-bismuth ± allicin[14], whilst Hu *et al*[46] compared ranitidine plus allicin to allicin alone[37]. Both therapeutic regimens are not wildly accepted and may have caused an unneglected bias risk. The study by Hu *et al*[46] performed an adequate search strategy, but the *H. pylori* patients had duodenal ulcers, which narrowed the application of the evidence.

This is the first systematic review and meta-analysis of *H. pylori* treatment using allicin that was assessed using the GRADE system, although the quality of main outcome was graded as "very low" due to downgrades for the risk of bias and indirectness. What's more, when considering this meta-analysis, potential limitations should be considered: (1) The included studies were of low quality, which limited the clinical evidence; (2) Although *I2* statistics assessment showed no statistical heterogeneity, we considered existence of clinical heterogeneity of the included studies. First, seven included studies included the participants with *H. pylori* infection combined with *H. pylori* related ulcers while the rest one[19] included the participants with *H. pylori* infection alone. Second, the present review compared the efficacy of allicin plus PTT/BCQT *vs* PTT/BCQT alone. However, the PTT/BCQT regimens of included studies differed, especially components of antibiotics. Third, most of the included studies (7/8, 87.50%) were performed in China except for the study by Kochar *et al*[19]. Fourth, the eradication therapy period of the included studies ranged from 7 d to 14 d; and (3) Antibiotic resistance of the participants was not assessed, so the efficacy of allicin on antibiotic resistant *H. pylori* strains was not assessed.

In conclusion, this study provides evidence that allicin improves eradication rates, healing rates, the remission of peptic ulcers, and the remission of abdominal pain, but does not affect side effects when used as an add-on treatment for *H. pylori* infection and *H. pylori* related ulcers. However, the quality of this study was graded as "very low" for eradication and side effects rates and "low" for healing and total remission rates of peptic ulcers. These results should be treated with cautions due to limited quality of the included studies.

Table 4 Subgroup analyses of healing rates of peptic ulcers

Comparison	Healing rate (%)		Heterogeneity		OR	95%CI	*P* value
	Allicin group	Control	I^2 (%)	*P* value			
Allicin + PTT *vs* PTT[15-18,20] (ITT)	80.32	68.29	0	0.527	2.14	1.39-3.29	0.001
Allicin + PTT *vs* PTT[15-18,20] (PP)	80.65	68.57	0	0.513	1.93	1.25-2.96	0.003
Allicin-PPI-B-T-C *vs* PPI-B-T-C[21,22] (ITT/PP)	95.51	87.82	22.924	0.255	2.83	1.13-7.10	0.026
Allicin-PPI-Am-F *vs* PPI-Am-F[15,18,20] (ITT/PP)	83.62	65.00	0	0.660	1.90	1.18-3.06	0.002

PPI: Proton pump inhibitor; PTT: Proton pump inhibitor triple therapy; Am: Amoxicillin; F: Furazolidone; C: Clarithromycin; T: Tinidazole; B: Bismuth potassium citrate tablets; ITT: Intent-to-treat analysis; PP: Pre-protocol analysis; OR: Odds ratio; CI: Confidence interval.

Table 5 Subgroup analyses of total remission rates of peptic ulcers

Comparison	Total remission rate (%)		Heterogeneity		OR	95%CI	*P* value
	Allicin group	Control	I^2 (%)	*P* value			
Allicin + PTT *vs* PTT[15,16,18,20] (ITT/PP)	93.12	81.48	0	0.844	3.13	1.51-6.51	0.004
Allicin-PPI-Am-F *vs* PPI-Am-F[15,18,20] (ITT/PP)	93.97	80.83	0	0.931	4.87	1.36-17.50	0.015

PPI: Proton pump inhibitor; PTT: Proton pump inhibitor triple therapy; Am: Amoxicillin; F: Furazolidone; C: Clarithromycin; T: tinidazole; B: Bismuth potassium citrate tablets; ITT: Intent-to-treat analysis; PP: Pre-protocol analysis; OR: Odds ratio; CI: Confidence interval.

Table 6 Subgroup analyses of side effect rates

Comparison	Side effect rate (%)		Heterogeneity		OR	95%CI	*P* value
	Allicin group	Control	I^2 (%)	*P* value			
Allicin + PTT *vs* PTT[17-20] (ITT)	7.38	13.51	6.66	0.36	0.52	0.22-1.20	0.125
Allicin + PTT *vs* PTT[17-20] (PP)	5.92	9.57	0	0.59	0.61	0.32-1.16	0.132
Allicin-PPI-B-T-C *vs* PPI-B-T-C[21,22] (ITT/PP)	4.49	5.77	0	0.69	0.77	0.28-2.13	0.612
Allicin-PPI-Am-F *vs* PPI-Am-F[18,20] (ITT/PP)	2.27	7.95	0	0.85	0.27	0.054-1.34	0.110

PPI: Proton pump inhibitor; PTT: Proton pump inhibitor triple therapy; Am: Amoxicillin; F: Furazolidone; C: Clarithromycin; T: Tinidazole; B: Bismuth potassium citrate tablets; ITT: Intent-to-treat analysis; PP: Pre-protocol analysis; OR: Odds ratio; CI: Confidence interval.

Table 7 Results of quality assessment

Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence
Eradication rate						
867(8 studies)	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	Undetected	Very low[12]
Healing rate of ulcers						
807(7 studies)	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Low[1]
Total remission rate of ulcers						
807(7 studies)	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Low[1]
Side effect rate						
549(5 studies)	Very serious[1]	No serious inconsistency	Serious[3]	No serious imprecision	Undetected	Very low[13]

[1]We downgraded by two levels because all included studies did not state random method although declared to be randomized. What's more, blinding of patients was not mentioned in all included studies and we preferred to identify these studies as non-blindness;
[2]The present systematic review mainly aimed to assess the efficacy with eradication rate as primary outcome in patients with *H. pylori* infection. However, the participants of seven included studies (7/8, 87.50%) included patients with *H. pylori* infection combined with peptic ulcers. Such difference might be another origin of bias;
[3]The present systematic review mainly aimed to assess the safety of allicin among patients with *H. pylori* infection. However, four included studies (4/5, 80.00%) included patients with *H. pylori* infection combined with peptic ulcers. Such difference might be another origin of bias.

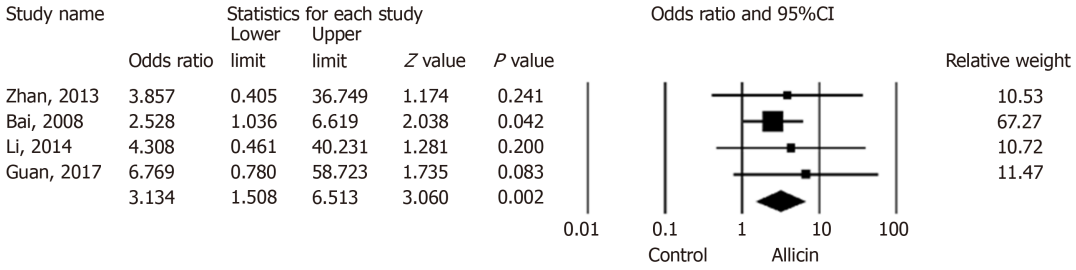

Figure 4 Total remission rates of peptic ulcers between allicin and control groups (intent-to-treat/per-protocol analysis). The total remission rate across allicin groups was significantly higher than that of the control group for ITT/PP analyses [95.99% (359/374) *vs* 89.25% (332/372), odds ratio = 3.13, 95% confidence interval: 1.51-6.51, *P* = 0.002]. CI: Confidence interval.

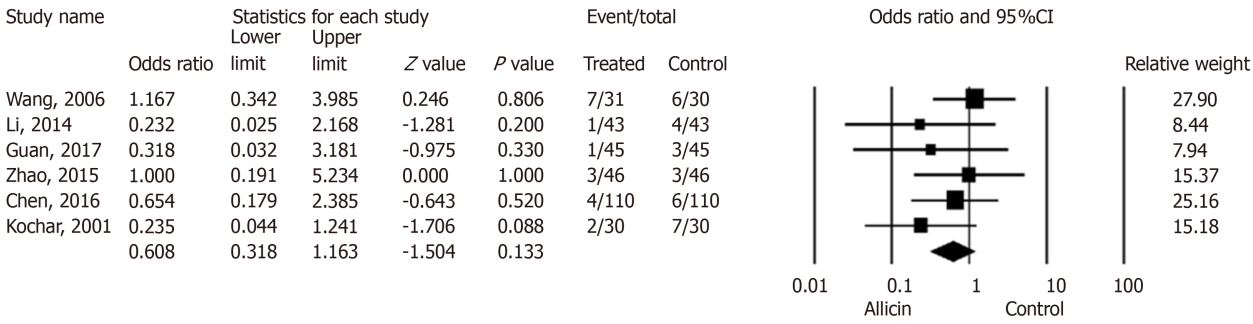

Figure 5 Side effect rates between allicin and control groups (intent-to-treat/per-protocol analysis). There was no statistical significance in side effect rates between the allicin group and control group for ITT analysis [5.90% (18/305) *vs* 9.53% (29/304), odds ratio = 0.61, 95% confidence interval: 0.32-1.16, *P* = 0.133]. CI: Confidence interval.

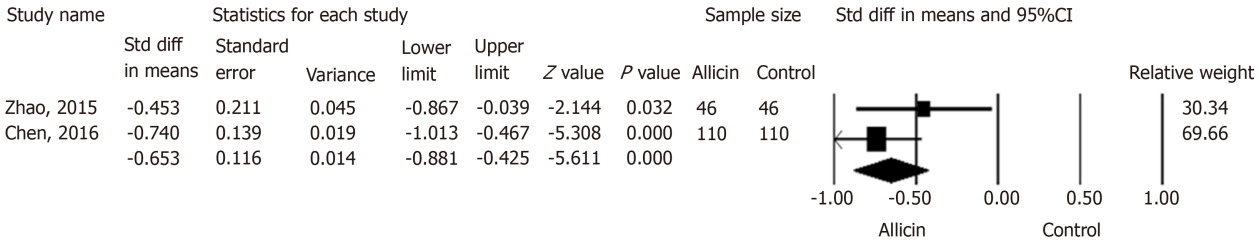

Figure 6 Abdominal pain disappearance times between allicin and control groups. Meta-analysis showed more rapid cessation of abdominal pain in the allicin group (standard mean difference = -0.653, 95% confidence interval: -0.88--0.43, $P < 0.001$). CI: Confidence interval; Std diff in means: Standard difference in means.

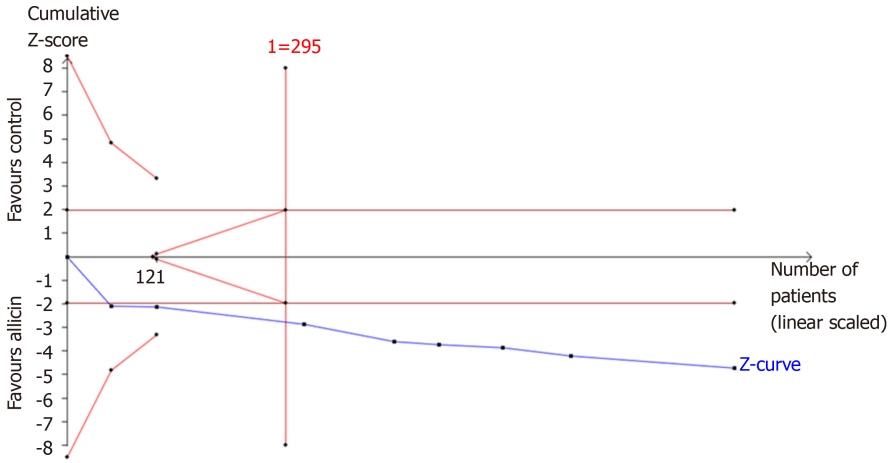

Figure 7 Trial sequential analysis of the eradication rates. Trial sequential analysis of the eradication rates showed that an information size of 295 participants was required. Cumulative Z-curve crossed the trial sequential monitoring boundary, showing significant evidence of eradication rates. The cumulative values of the *Z* scores crossed conventional boundary values, trial sequential monitoring boundaries, and RIS line, suggesting that the trials were sufficient, and no alterations of the conclusions were likely.

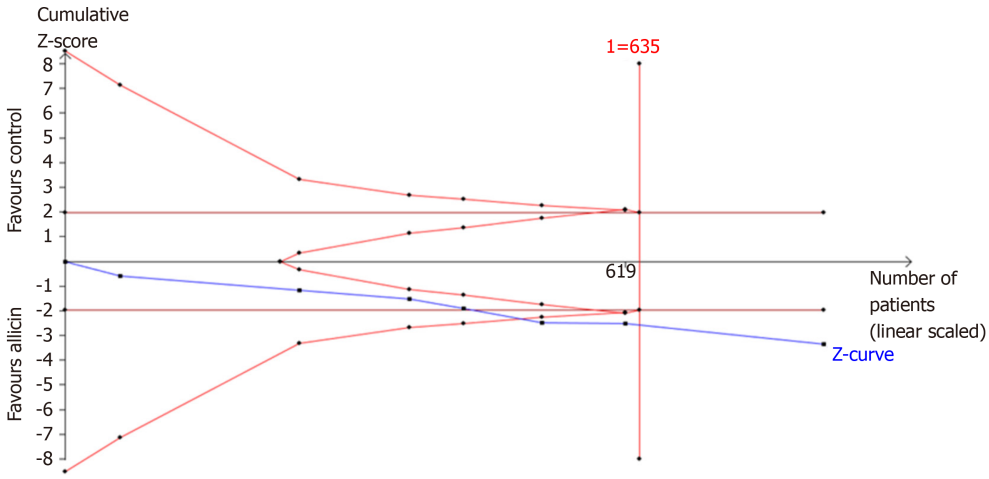

Figure 8 Trial sequential analysis of the healing rates of peptic ulcers. Trial sequential analysis of the healing rates showed that an information size of 635 participants was required. Cumulative Z-curve crossed the trial sequential monitoring boundary, showing significant evidence of eradication rates. The cumulative values of the Z scores crossed conventional boundary values, trial sequential monitoring boundaries, and RIS line, suggesting that the trials were sufficient, and no alterations of the conclusions were likely.

ARTICLE HIGHLIGHTS

Research background

Allicin (2-propene-1-sulfinothioic acid S-2-propenyl ester, diallyl thiosulfinate), a compound of garlic, was proved to be active in inhibiting *Helicobacter pylori* (*H. pylori*) growth *in vitro*. However, several clinical trials using garlic oil and fresh oral garlic failed to show improvements

in *H. pylori* infection. In recent years, due to developments in pharmaceutical technology, commercial allicin tablets are available, with a series of randomized clinical trials that explored allicin as an add-on therapy to PPI therapy or bismuth containing quadruple therapy to treat *H. pylori* infection.

Research motivation
Allicin as an add-on therapy to treat *H. pylori* infection has been trialed, with variable results. Whether allicin could be medicated as an anti-*H. pylori* drug is still inconclusive.

Research objectives
We performed a meta-analysis to evaluate the efficacy and safety of allicin as an add-on therapy, *i.e.*, allicin plus PPI triple therapy or bismuth containing quadruple therapy for *H. pylori* infection.

Research methods
Electronic databases including MEDLINE, EMBASE, Web of Science, *etc*. were searched. A meta-analysis was performed using the fixed-effects model for low heterogeneity and the random-effects model for high heterogeneity with sensitivity analysis. Bias was evaluated using Egger's tests. Trial sequential analysis (TSA) was used to evaluate information size and treatment benefits. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the level of quality.

Research results
A total of eight RCTs consisting of 867 participants were included. As a result, add-on therapy of allicin combined with PPI triple therapy (PTT) or bismuth containing quadruple therapy (BCQT) showed a significantly higher eradication rate (93.33% *vs* 83.56%, $P < 0.001$) and healing rates of ulcer (86.17% *vs* 75.87%, $P < 0.001$). In addition, the total remission rate of peptic ulcers across all allicin groups was significantly higher than that of controls (95.99% *vs* 89.25%, $P = 0.002$). Such outcomes were graded as "low" (ulcer healing rates and total ulcer remission rates) or "very low" (eradication rates and side effects rates) according to the GRADE assessment.

Research conclusions
This study provides evidence that allicin improves eradication rates, healing rates, the remission of peptic ulcers, and the remission of abdominal pain, but does not affect side effects when used as an add-on treatment for *H. pylori* infection and *H. pylori* related ulcers. In other words, allicin plus PPI triple therapy or bismuth containing quadruple therapy may obtain better therapeutic effects.

Research perspectives
The present review evaluated the efficacy and safety of allicin as an add-on therapy for *H. pylori* infection, with conclusion that allicin might improve healing rate and symptom remission of *H. pylori* related ulcers as well as *H. pylori* eradication rate. However, there are still many questions remaining unclear. On one hand, the exact mechanism of allicin as an anti-*H. pylori* drug is not clear up till now. On the other hand, further clinical evidence of high quality is still needed since the present evidence is of "low" or "very low" quality.

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