


# Curcumin and proton pump inhibitors for functional dyspepsia: a randomised, double blind controlled trial

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10.1136/bmjebm-2022-112231

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bmjebm-2022-112231>).

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**To cite:** Kongkam P, Khongkha W, Lopimpisuth C, *et al.* *BMJ Evidence-Based Medicine* Epub ahead of print: [please include Day Month Year]. doi:10.1136/bmjebm-2022-112231

## Abstract

**Objective** To compare the efficacy of curcumin versus omeprazole in improving patient reported outcomes in people with dyspepsia.

**Design** Randomised, double blind controlled trial, with central randomisation.

**Setting** Thai traditional medicine hospital, district hospital, and university hospitals in Thailand.

**Participants** Participants with a diagnosis of functional dyspepsia.

**Interventions** The interventions were curcumin alone (C), omeprazole alone (O), or curcumin plus omeprazole (C+O). Patients in the combination group received two capsules of 250mg curcumin, four times daily, and one capsule of 20mg omeprazole once daily for 28 days.

**Main outcome measures** Functional dyspepsia symptoms on days 28 and 56 were assessed using the Severity of Dyspepsia Assessment (SODA) score. Secondary outcomes were the occurrence of adverse events and serious adverse events.

**Results** 206 patients were enrolled in the study and randomly assigned to one of the three groups; 151 patients completed the study. Demographic data (age 49.7±11.9 years; women 73.4%), clinical characteristics and baseline dyspepsia scores were comparable between the three groups. Significant improvements were observed in SODA scores on day 28 in the pain (−4.83, −5.46 and −6.22), non-pain (−2.22, −2.32 and −2.31) and satisfaction (0.39, 0.79 and 0.60) categories for the C+O, C, and O groups, respectively. These improvements were enhanced on day 56 in the pain (−7.19, −8.07 and −8.85), non-pain (−4.09, −4.12 and −3.71) and satisfaction (0.78, 1.07, and 0.81) categories in the C+O, C, and O groups, respectively. No significant differences were observed among the three groups and no serious adverse events occurred.

**Conclusion** Curcumin and omeprazole had comparable efficacy for functional dyspepsia with no obvious synergistic effect.

**Trial registration number** TCTR20221208003.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Dyspepsia is a common disorder and patients usually try behavioural and diet modifications, and over-the-counter drugs before seeing a physician.
- ⇒ Proton pump inhibitors have been established as an effective treatment for functional dyspepsia.
- ⇒ Curcumin, an active ingredient in turmeric, is currently used for the treatment of dyspepsia in countries in Southeast Asia but there is still uncertainty.

## WHAT THIS STUDY ADDS

- ⇒ In this double blind, placebo controlled clinical trial, oral curcumin was found to be safe and well tolerated.
- ⇒ Patients with functional dyspepsia treated with curcumin, curcumin plus omeprazole and omeprazole had similar significant symptomatic improvement.
- ⇒ There was no synergistic effect detected between omeprazole and curcumin.

## Introduction

Functional dyspepsia is a frequently occurring disorder that can be caused by a variety of factors, with no evidence of other structural diseases that exhibit similar symptoms. Although dyspepsia is common, many patients do not schedule an appointment with a doctor to treat this condition. A quarter of patients with dyspepsia have symptoms that require specific treatment, while the rest

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

- ⇒ This study provides possible evidence for additional drug options for patients with functional dyspepsia.
- ⇒ More clinical trials are required to assess long term outcomes and adverse events.

do not have symptoms that define them as functional dyspepsia.<sup>1</sup> According to the Rome IV criteria, patients diagnosed with functional dyspepsia have postprandial fullness, early satiation, epigastric pain or burning, and no evidence of structural disease to explain the symptoms. Postprandial distress syndrome and epigastric pain syndrome are two types of functional dyspepsia.<sup>2</sup>

In a primary care setting, the initial approach for managing functional dyspepsia typically involves a combination of behavioural and dietary modifications, as well as over-the-counter medications. Behavioural and dietary modifications aim to address triggers and lifestyle factors that may contribute to the symptoms. Over-the-counter proton pump inhibitors (PPIs) are commonly recommended in several countries as a first line medication, but patients with persistent symptoms may require further medical attention to explore the possibility of *Helicobacter pylori* infection.<sup>3-5</sup> The Cochrane systematic review on the use of PPIs for functional dyspepsia, conducted recently, demonstrated superior overall effectiveness compared with placebo, with a number needed to treat of 11.<sup>6</sup> However, prolonged use of PPIs demonstrated a potential increased risk of fractures, micronutrient deficiencies, and infection. The controversial nature of these potential adverse effects persists due to the absence of higher quality study.<sup>7-9</sup>

Turmeric, scientifically known as *Curcuma longa* L., has a long history of extensive use. This plant has a valuable active compound, curcumin, which is used both topically and orally for medicinal purposes. While curcumin is commonly found in nourishing creams and cosmetics, it is also available in the form of powder capsules used for treating various gastrointestinal problems, including dyspepsia. Recent findings from a Cochrane review suggested that curcumin may offer moderate improvement in dyspepsia symptoms compared with placebo.<sup>10</sup> However, there is currently a lack of head-to-head evidence comparing the efficacy of curcumin with conventional drugs.

Among the Thai population and individuals residing near Thailand, turmeric is frequently used to alleviate dyspepsia-like symptoms. However, conventional physicians have been hesitant to consider this herbal medicine as the primary treatment for functional dyspepsia, mainly due to a lack of research comparing the effectiveness and side effects of curcumin with PPIs. This study aimed to compare the efficacy of curcumin with a PPI in the treatment of patients with functional dyspepsia.

**Methods****Study design**

This multicentre, randomised, double blind, placebo controlled, parallel group equivalence trial was conducted at the Thai Traditional Medicine Institute and Chao Phraya Abhaibhubejhr Hospital from January 2019 to 2021. Patients participating in the trial were assigned randomly to one of three groups: curcumin plus omeprazole (C+O), curcumin only (C only), and omeprazole

only (O only). The study findings were reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines and the CONSORT Herbal Extension.<sup>11</sup>

**Study population**

Patients who were willing to participate in this trial were evaluated for eligibility: symptoms compatible with functional dyspepsia, as defined by the Rome IV criteria,<sup>12</sup> age 18–70 years, Eastern Cooperative Oncology Group performance status 0 or 1 (indicating good overall health), no use of aspirin or non-steroidal anti-inflammatory drugs within the past 3 months, no consumption of curcumin or curcumin-rich food (approximately 250 mg daily) in the 4 weeks preceding the study, absence of symptoms related to irritable bowel syndrome (such as constipation, diarrhoea and frequent defecation), no usage of herbal medications or medications that can affect gastrointestinal symptoms or diseases, and no intake of PPIs within the 4 weeks preceding the study. Exclusion criteria were: pregnancy or breastfeeding; allergy to curcumin; presence of gallstones; severe inflammation of the gastric mucosa, oesophageal mucosa or intestinal mucosa; previous infection with gastric *H pylori*; coexistence of diseases that could hinder the treatment of functional dyspepsia; or presence of symptoms or physical signs indicating serious diseases inconsistent with functional dyspepsia. To confirm the diagnosis of functional dyspepsia, all participants underwent gastroscopy, ensuring accurate categorisation of patients in the study based on their medical condition.

**Randomisation and blinding**

Participants were recruited at the Institute of Thai Traditional Medicine, Department of Thai Traditional and Alternative Medicine, Ministry of Public Health, Bangkok, Thailand, and Chao Phraya Abhaibhubejhr Hospital, a tertiary care hospital in Prachinburi, Thailand. Eligible participants were randomly allocated to one of the three groups using a block randomisation of size six at a ratio of 1:1:1. Identification numbers were generated and inserted into the opaque concealed envelope by researchers from the Institute of Thai Traditional Medicine, who were not involved in the care of the volunteers. Clinicians, data collectors and patients were blinded during this entire process. The randomisation identification number was assigned to the three groups with the code of each participant and delivered in sealed envelopes to the doctor conducting the research in the area.

**Recruitment**

Several methods were used to recruit participants for this study. The recruitment strategies included: patient recruitment through physicians in both participating institutions, utilisation of electronic and printed media, promotional flyers, communication with physicians and publicising the study in healthcare facilities that offer both conventional and traditional Thai medicine services.

**Treatment and safety protocol**

The herbal medicinal product used in this trial was curcumin, a natural compound derived from turmeric, also known as *Curcuma longa* L. It was administered in the form of powder capsules containing 250 mg of curcumin. Before initiation, the curcumin capsules underwent qualitative testing to ensure their quality, purity and compliance with regulatory standards. Rigorous measures were taken to confirm the presence of curcumin and the absence of any impurities or contaminants by the Herb and Thai Traditional Medicine Development, Department of Thai Traditional and Alternative Medicine, Ministry of Public Health. Placebo

capsules, identical in appearance to the curcumin or omeprazole capsules but devoid of the active ingredient, were also used.

At the beginning of the trial, each group of enrolled participants received their assigned medications in person at both research sites. The medications were carefully packaged into two different sizes: large capsules containing 250 mg of curcumin or placebo, and small capsules containing 20 mg of omeprazole or placebo. To ensure consistent dosing, each participant was provided with specific instructions to take two large capsules four times a day, along with one small capsule once a day, for a total duration of 28 days. While the four times daily regimen may raise concerns about compliance, it was chosen based on the recommendation provided by the National List of Herbal Medicine committee.

Qualified practitioners, experienced in the management of gastrointestinal disorders, oversaw the administration of the assigned medications. They provided clear instructions regarding the dosage regimen and addressed any queries or concerns raised by the participants throughout the trial. The inclusion of qualified practitioners ensured proper guidance and support for the participants, further enhancing the integrity of the study.

Patients were encouraged to report any potential side effects throughout the duration of the study. Additionally, formal assessment for possible adverse events were conducted on day 28. The study used the following discontinuation criteria: (1) participants with allergies or inability to take the medication, (2) participants who did not complete the treatment evaluation follow-up, (3) participants unable to tolerate the medication side effects, (4) compatibility of pathological examination results with specific cancers or tumours in the oesophagus, stomach or duodenum and (5) unsuccessful completion of the endoscopy procedure. The criteria for terminating the study encompassed two aspects: (1) serious adverse events exceeding 3% or occurring in six or more participants, triggering a review by the ethics committee to determine the necessity of discontinuing the research and (2) any concerns or significant ethical lapses identified during the research process.

### Outcome measurements

At the start of the study, the extent of the symptoms experienced by the participants was assessed using two validated questionnaires: the Short-Form Leeds Dyspepsia Questionnaire (SF-LDQ) and the Severity of Dyspepsia Assessment (SODA). Initially, both the SF-LDQ and SODA were used to comprehensively evaluate the symptoms present at baseline. However, during the course of the trial, measurement of symptom severity on day 28 and day 56 was conducted only with the SODA questionnaire. The SODA questionnaire was specifically chosen to observe and quantify the changes in symptom severity over time. To ensure accurate and consistent data collection, each measurement was carried out in the clinical setting. However, on day 56, the assessment was conducted by telephone interview, enabling convenient and efficient data gathering while maintaining the integrity of the study.

Our study also aimed to evaluate the occurrence of adverse events related to the treatments, with a specific emphasis on monitoring liver function. To assess any potential changes in liver function during the treatment period, we conducted liver function tests (LFTs) on day 1 and day 28. However, LFTs were not performed on day 56. Nonetheless, on day 28, after the intervention period, patients underwent a detailed interview to identify and document any adverse events or undesirable occurrences that may have arisen during the course of the treatment.

### Sample size calculation

The sample size calculation for this study used an equivalence design, utilising a two tailed test to examine the comparability between the treatment groups.<sup>13</sup> The investigator defined a desired improvement of 2 points in the SODA score between the treatment group, assuming an SD of 4. The significance level and power of the test were set at 0.05 and 0.80, respectively. Based on these parameters, the initial sample size estimate per group was calculated to be 63 individuals. This estimate took into account potential loss to follow-up during the study and the possibility of detecting additional disorders during endoscopy, which was anticipated to occur in approximately 10% of participants. To account for these factors and maintain adequate statistical power, we ultimately determined a sample size of 70 individuals per group, ensuring a sufficient number of participants for meaningful analysis and robust conclusions.

### Statistical analysis

Data analysis was performed with Stata/MP statistical software release 15 (StataCorp, College Station, Texas, USA). Descriptive statistics were used to summarise the data. Continuous variables are reported as mean (SD), while categorical variables were summarised as frequencies (percentages). An intention-to-treat analysis was performed, and all subjects were included in the analysis in the group to which they were randomised. To assess differences in baseline characteristics between treatment groups, the  $\chi^2$  test and analysis of variance (ANOVA) were used. To examine the associations between the treatment groups and outcomes, repeated measures ANOVA with a Greenhouse–Geisser correction and the generalised estimating equation were used. Subgroup analysis was performed for SODA non-pain symptoms. A significance level of  $p < 0.05$  was considered for all statistical analyses. In handling missing data due to loss of follow-up, the last observation carried forward method was used. This approach involved replacing missing values of participants who dropped out with their last available measurement. It was assumed that the participants' responses would have remained stable from the point of dropout until completion of the trial, without experiencing further improvement or decline.

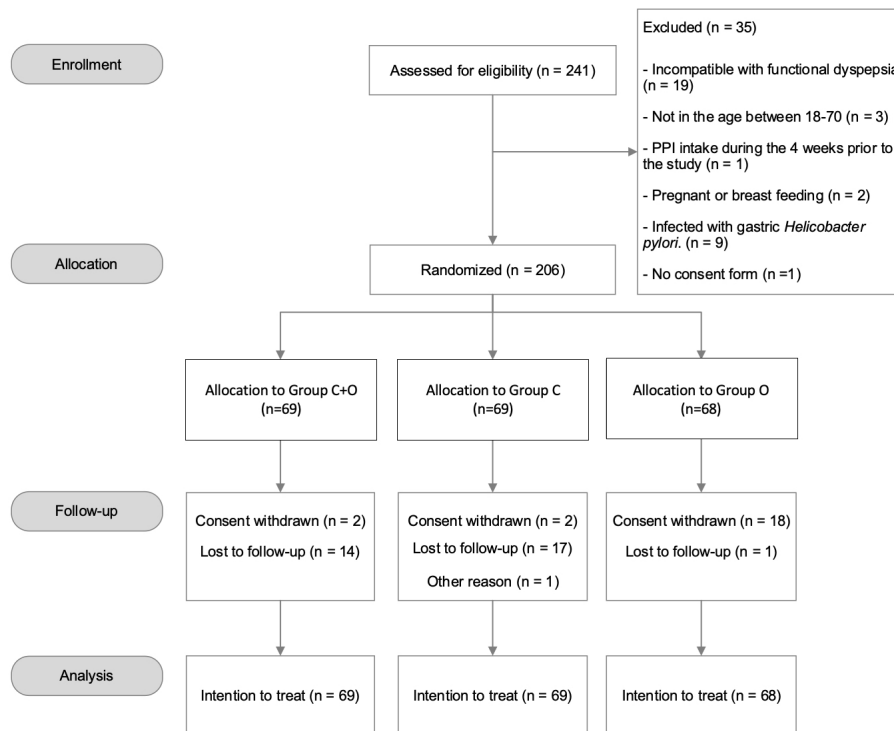
### Results

The recruitment phase for this study commenced on 27 June 2019, and the follow-up period concluded on 31 January 2020. A total of 241 patients were evaluated for eligibility; of these, 206 met the inclusion criteria and were enrolled and randomised to one of the three groups. The most common reason for ineligibility was incompatibility with the diagnosis of functional dyspepsia, followed by incorrect age, recent intake of PPI, being pregnant or breastfeeding, current *H pylori* infection and rejection of consent.

Overall, 69, 69 and 68 patients were randomly assigned to the C+O, C, and O groups; of these, 16, 20, and 19 dropped out, respectively. Detailed numbers and explanations for exclusion and dropout are shown in the CONSORT diagram (figure 1). Baseline demographic and clinical characteristics were similar in the C+O, C, and O groups (table 1).

### Dyspepsia symptom severity

At baseline, SF-LDQ did not show significant differences, whereas the overall SODA scores (pain intensity, non-pain symptoms and satisfaction) were comparable between the three groups (table 2). On day 28, a significant improvement in SODA pain intensity and non-pain symptoms scores was observed in the three groups:



**Figure 1** CONSORT (Consolidated Standards of Reporting Trials) diagram. C, curcumin only; C+O, curcumin plus omeprazole; O, omeprazole only; PPI, proton pump inhibitor.

pain intensity decreased by  $-4.83$  (95% CI  $-6.69$  to  $-2.96$ ),  $-5.46$  ( $-7.33$  to  $-3.06$ ) and  $-6.22$  ( $-8.10$  to  $-4.34$ ) in the C+O, C and O groups, respectively, while non-pain symptoms decreased by  $-2.22$  ( $-3.05$  to  $-1.38$ ),  $-2.32$  ( $-3.15$  to  $-1.48$ ) and  $-2.31$  ( $-3.15$  to  $-1.47$ ) in the C+O, C and O groups, respectively. In contrast, SODA satisfaction scores significantly improved by  $0.79$  (95% CI  $0.03$  to  $1.56$ ) only in group C.

No significant difference was found between the three groups. The data collected at each visit and for each factor indicated that there was no significant difference observed between the three groups (online supplemental table 1). Comparison of day 0 with day 56 showed a significant improvement in each category of SODA scores: pain  $-7.19$  (95% CI  $-9.06$  to  $-5.32$ ),  $-8.07$  ( $-9.94$  to  $-6.21$ ) and  $-8.85$  ( $-10.73$  to  $-6.97$ ); non-pain  $-4.09$  ( $-4.92$  to  $-3.25$ ),  $-4.12$  ( $-4.95$  to  $-3.28$ ) and  $-3.71$  ( $-4.55$  to  $-2.86$ ); and satisfaction  $0.78$  ( $0.02$  to  $1.55$ ),  $1.07$  ( $0.30$  to  $1.84$ ) and  $0.81$  ( $0.04$  to  $1.58$ ) in the C+O, C and O groups, respectively. Additionally, comparison of day 28 with day 56 revealed positive changes in each category. The exhaustive numbers for each SODA score are available in online supplemental table 2. The results of the subgroup analysis of the SODA scores on non-pain symptoms, divided according to item 7 to item 13, are available in online supplemental table 3. Figures 2–4 show the changes in SODA scores based on pain intensity, non-pain symptoms and satisfaction, respectively. Summary statistics are displayed as mean (95% CI).

Analysis of SODA scores by a generalised estimating equation did not show significant differences between the C+O group versus the C group, the C+O group versus the O group, and the C group versus the O group (table 3).

#### Adverse events

Adverse events included anxiety, diarrhoea, drowsiness, flatulence, headache and vomiting. In group C+O, these occurred in

two patients (2.90%), including one diarrhoea (1.45%), one drowsiness (1.45%), one headache (1.45%) and one vomiting (1.45%). In group C only, these occurred in three patients (4.35%), including one incident of anxiety (1.45%), one diarrhoea (1.45%), one flatulence (1.45%) and one vomiting (1.45%). No serious adverse events took place.

In this study, we observed that at baseline, approximately 25% of all patients had impaired LFTs. Online supplemental table 4 presents comparison of liver enzyme levels before and after treatment across the three groups. On day 28, 36.23% of patients in group C+O, 37.68% of patients in group C and 29.41% in group O had impaired LFTs. Although differences in deterioration in LFTs between the groups did not reach statistical significance, there was a clear trend towards LFT impairment in curcumin users.

#### Discussion

Curcumin, extracted from turmeric, is a hydrophobic polyphenol with a low molecular weight. This compound exhibits a broad range of biological properties, such as anti-inflammatory, antioxidant, antiproliferative and antimicrobial properties. Several clinical trials have established the pharmacological properties of curcumin. However, the mechanisms underlying symptom generation in patients with functional digestive disorders remain poorly understood, as no mucosal injury has been identified to explain their distressing symptoms.<sup>14</sup> Transient receptor potential vanilloid type 1 (TRPV1) receptors have been shown to play a critical role in the detection and transmission of somatic and visceral nociceptive neural signals,<sup>15</sup> and have been implicated in the induction of symptoms in these diseases. TRPV1 is a multimodal sensory transducer that can be activated by a variety of harmful stimuli, including heat, low pH, endogenous lipid derivatives such as anandamide, and exogenous vanilloid containing substances such as capsaicin.<sup>16</sup> In particular, curcumin shares the same vanilloid ring moiety as capsaicin, making TRPV1 a likely target, and



**Table 1** Characteristics of participants in the curcumin plus omeprazole (C+O), curcumin only (C) and omeprazole only (O) groups

Characteristics	C+O (n=69)	C only (n=69)	O only (n=68)
<b>Demographics</b>			
Women (n (%))	49 (71.01)	50 (72.46)	52 (76.47)
Age (years)	49.54±12.10	49.97±11.96	49.3±11.65
Height (cm)	159.03±8.62	158.8±9.01	159.04±7.56
Weight (kg)	62.13±12.19	62.71±13.38	63.43±12.36
Body mass index (kg/m <sup>2</sup> )	24.44±3.56	24.79±4.43	25.05±4.39
<b>Vital signs</b>			
Pulse rate (beats/min)	78.19±12.01	78.38±8.41	80.82±10.24
Respiratory rate (beats/min)	19.22±1.46	20.03±7.51	19.12±1.40
Body temperature (°C)	36.82±0.37	36.81±0.27	36.85±0.26
Systolic blood pressure (mm Hg)	128.36±13.85	129.96±14.37	126.15±16.13
Diastolic blood pressure (mm Hg)	77.65±10.96	78.58±9.69	75.96±10.48
<b>Dyspepsia group (n (%))</b>			
Postprandial distress syndrome	43 (63.24)	42 (60.87)	46 (67.65)
Epigastric pain syndrome	25 (36.76)	27 (39.13)	22 (32.35)
<b>Laboratory</b>			
White blood cells (cells/mm <sup>3</sup> )	6914.48±2107.40	7401.08±2199.63	7710.48±2540.89
Haemoglobin (g/dL)	13.56±2.87	12.90±1.40	12.42±1.87
Haematocrit (%)	40.04±5.15	39.24±3.16	39.12±4.46
Platelet count (cells/mm <sup>3</sup> )	260 000±57 830.24	250 000±55 400.04	270 000±93 237.94
AST (SGOT) (U/L)	26.76±9.81	27.90±13.38	25.43±7.89
ALT (SGPT) (U/L)	25.48±16.96	25.64±16.19	28.22±22.11
Total bilirubin (mg/dL)	1.11±2.89	1.07±2.91	1.04±3.45
International normalised ratio	0.95±0.15	0.99±0.12	0.99±0.10
Creatinine (mg/dL)	0.81±0.38	0.89±0.59	0.91±1.05
Sodium (mmol/L)	139.5±2.10	139.81±2.38	137.59±16.22
Potassium (mmol/L)	3.96±0.43	3.81±0.43	3.92±0.35
Chloride (mmol/L)	104.08±4.37	103.77±3.90	103.50±3.38
Total carbon dioxide (mmol/L)	24.76±2.93	25.61±6.98	25.08±3.32
Values are mean±SD unless indicated otherwise.			
ALT, alanine aminotransferase; AST, aspartate aminotransferase; SGOT, serum glutamic–oxaloacetic transaminase; SGPT, serum glutamic–pyruvic transaminase.			

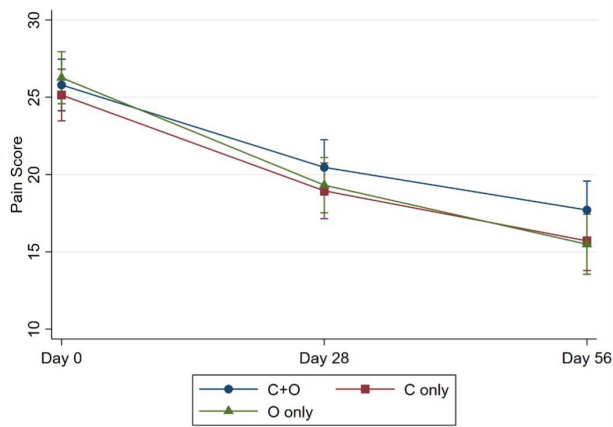
it has been shown in animals that curcumin inhibits capsaicin induced TRPV1 activation competitively.<sup>17</sup>

Increased TRPV1 signalling has been suggested to contribute to visceral hypersensitivity in functional gastrointestinal diseases, including oesophageal hypersensitivity.<sup>17</sup> Additionally, TRPV1 receptors are highly expressed throughout the gastrointestinal tract and enteric nervous system, and there is evidence that curcumin can inhibit gastrointestinal nociception and reverse

intestinal hypersensitivity through peripheral terminals. With this mechanism of action in mind, it cannot be ruled out that this molecule may be beneficial in the treatment of patients with functional dyspepsia and irritable bowel syndrome, which are disorders that remain clinically challenging in the presence of currently available medications and whose patients may benefit from curcumin's pharmacological properties on TRPV1 as a novel pain modulator.

**Table 2** Baseline Short-Form Leeds Dyspepsia Questionnaire (SF-LDQ) and Severity of Dyspepsia Assessment (SODA) scores in the curcumin plus omeprazole (C+O), curcumin only (C) and omeprazole only (O) groups

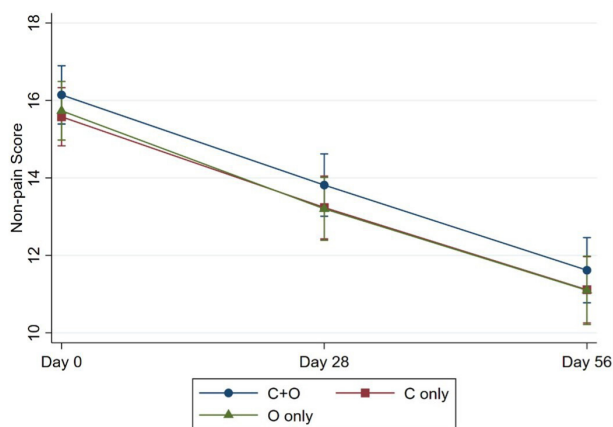
Factor	C+O (n=69)	C only (n=69)	O only (n=68)
<b>SODA</b>			
Pain intensity (2–47)	25.80±3.22	25.14±4.09	26.26±3.74
Non-pain symptoms (7–35)	16.14±3.18	15.58±3.21	15.74±2.69
Satisfaction (2–23)	11.78±1.98	11.84±1.65	11.68±2.29
<b>SF-LDQ</b>			
Method 1 (sum frequency)	7.90±4.23	7.01±4.06	7.12±3.56
Method 2 (sum severity)	7.97±4.25	6.88±4.14	6.85±3.65
Method 3 (total)	15.87±8.44	13.90±8.16	13.96±7.20
Method 4 (highest frequency)	3.16±1.15	3.20±1.02	3.41±0.80
Method 5 (highest severity)	3.19±1.18	3.19±1.03	3.31±0.87
Values are mean±SD.			



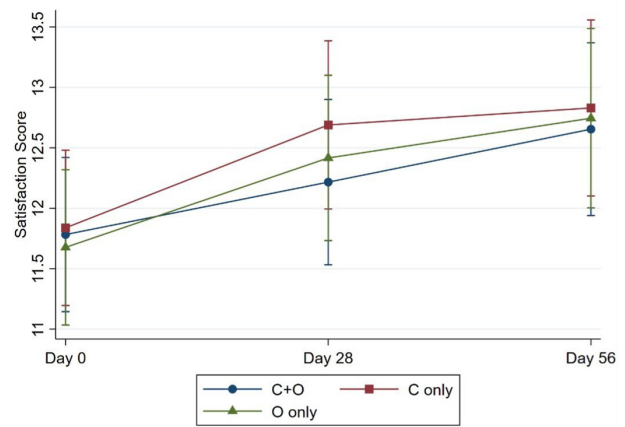
**Figure 2** Comparative changes in Severity of Dyspepsia Assessment (SODA) pain scores in the curcumin plus omeprazole (C+O), curcumin alone (C) and omeprazole alone (O) groups.

Curcumin has been clinically studied in patients with inflammatory bowel disease, irritable bowel syndrome, ulcers, *H pylori* infections and even pancreatitis. Although early experimental studies did not confirm the eradication effect of *H pylori*,<sup>18</sup> more recent meta-analyses have demonstrated the potential additional benefits of polyphenol compounds when used in conjunction with standard triple therapy for *H pylori* eradication.<sup>19</sup> Curcumin is effective in the treatment of gastric ulcers, erosions and dyspepsia,<sup>20, 21</sup> with ulcers and erosions reduced or even eradicated after administration of curcumin (3000 mg/day) for up to 12 weeks, while abdominal pain and discomfort were significantly reduced. This explains why in this study we compared curcumin with a PPI as a treatment for functional dyspepsia.

Similarly to the findings of the current study, curcumin has been shown to be safe in numerous human studies, with only minor toxicity associated with this polyphenol.<sup>22</sup> Velayudhan *et al* documented the traditional use of curcumin and noted that even a single oral dose of up to 8000 mg was not detected in serum.<sup>23</sup> Therefore, curcumin is increasingly being viewed as a biomolecule capable of being administered for an extended period without causing adverse effects.<sup>24</sup> After 72 hours, safety was assessed in a dose increase study involving 34 healthy volunteers who received



**Figure 3** Comparative changes in Severity of Dyspepsia Assessment (SODA) non-pain scores in the curcumin plus omeprazole (C+O), curcumin alone (C) and omeprazole alone (O) groups.



**Figure 4** Comparative changes in Severity of Dyspepsia Assessment (SODA) satisfaction scores in the curcumin plus omeprazole (C+O), curcumin alone (C) and omeprazole alone (O) groups.

curcumin doses ranging from 500 to 12000 mg. Only seven subjects reported mild disturbances, including headache, skin rash, diarrhoea and yellow stool.<sup>25</sup> Another study, which lasted 1–4 months, found that increasing the dose of curcumin from 0.45 to 3.6 g/day resulted in rare cases of nausea and diarrhoea, as well as increased alkaline phosphatase and lactate dehydrogenase.<sup>26</sup> Some patients treated with doses as high as 8 g/day for 2 weeks complained of abdominal pain and bulky size.<sup>27</sup> The findings of the current study confirmed the safety of curcumin compared with PPIs when used to treat functional dyspepsia.

The Cochrane Database of Systematic Reviews demonstrated that PPI was more effective than placebo in the treatment of functional dyspepsia, regardless of the dose or duration of treatment.<sup>6, 28</sup> The presence of reflux symptoms or different subtypes of functional dyspepsia had no influence on the effect of PPI over placebo. PPIs may be slightly more effective in alleviating general symptoms of dyspepsia than H2RA and prokinetics. However, several previous studies have demonstrated adverse events associated with long term PPI use.<sup>29, 30</sup> Therefore, trials are required to examine the longer term benefits and harms (at least 6–12 months) of PPIs in functional dyspepsia. To expand the treatment options for patients with functional dyspepsia, we decided to compare PPI and curcumin in this study. The findings of the current study indicate that there were no significant adverse events associated with the short term use of PPI and curcumin.

We observed that despite improvements in pain and non-pain scores, there was no significant improvement in the SODA satisfaction scores in the O and C+O groups (table 3). A possible explanation for this observation could be related to the taste and/or smell of curcumin, which might have caused reduced pleasantness for the participants while ingesting it. This potential discomfort could offset the improvements in pain and non-pain symptoms, leading to the non-significant change in satisfaction score. Further studies may be needed to explore this hypothesis as well as to improve the palatability of curcumin.

To the best of our knowledge, this study represents the first head-to-head comparison demonstrating the efficacy of curcumin in treating functional dyspepsia compared with omeprazole. Curcumin was effective in all subtypes of functional dyspepsia. Curcumin and omeprazole were both effective for functional dyspepsia and did not appear to have a synergistic effect. The most recent dyspepsia guidelines from Thailand (2018)<sup>28</sup> recommended that patients with undiagnosed dyspepsia who do not have alarm

**Table 3** Pairwise comparison of Severity of Dyspepsia Assessment (SODA) scores in the curcumin plus omeprazole (C+O), curcumin only (C) and omeprazole only (O) groups

SODA scores	C+O vs C only (95% CI)	P value*	C+O vs O only (95% CI)	P value*	C only vs O only (95% CI)	P value*
Pain intensity (2–47)	–1.16 (–2.95 to 0.64)	0.206	–0.55 (–2.35 to 1.25)	0.548	0.61 (–1.19 to 2.41)	0.509
Non-pain symptoms (7–35)	–0.61 (–1.42 to 0.21)	0.143	–0.31 (–1.13 to 0.50)	0.452	0.30 (–0.52 to 1.11)	0.478
Satisfaction (2–23)	0.28 (–0.34 to 0.90)	0.383	–0.03 (–0.65 to 0.59)	0.933	–0.30 (–0.93 to 0.32)	0.340

\*Generalised estimating equation.

symptoms should receive an empirical trial of PPI for 4–8 weeks as first line therapy. Prokinetic agents may be used in patients with unexplained dyspepsia who do not improve after empirical PPI therapy. Furthermore, prokinetic agents, tricyclic antidepressants and cytoprotective agents have been shown to improve symptoms in patients with functional dyspepsia after failure of PPI therapy. Although this guideline did not specifically mention curcumin as a treatment option for functional dyspepsia, the new findings from our study may justify considering curcumin in clinical practice.

This multicentre randomised controlled trial provides highly reliable evidence for the treatment of functional dyspepsia. PPIs, widely used and approved for over-the-counter use, were compared with curcumin, a popular herbal remedy. The study design, including double blind randomisation, minimised biases. Participants met strict criteria, underwent endoscopy and were tested for *H pylori* infection. Furthermore, we implemented measures to minimise biases by ensuring that the individuals administering the drugs, participants receiving the drugs and individuals conducting the assessment remained blinded to the type of medications administered to the participants. The trial was carried out in hospitals, and certified individuals used standardised questionnaires for assessments. Statistical methods were appropriate and followed accepted principles.

Two follow-up appointments were scheduled, and blood tests showed no abnormal symptoms or liver function abnormalities. However, participants with high body mass index indicated a trend towards liver function impairment in the curcumin group, suggesting the need for larger studies. Some participants did not provide follow-up information, which is a study weakness. However, the number of participants who provided this information was sufficient for statistical analysis and the majority of the participants attended the follow-up visit. Therefore, it can be deduced from the results that even if the number of participants followed after drug administration increased, the study findings would not be significantly different. Another limitation of this study was the absence of long term follow-up data for all patients after treatment. This is a question that will require further investigation.

The strength of the study lies in its relevance to daily clinical practice, providing additional drug options in addition to PPIs alone, without added side effects. The study was unbiased, partially funded by government organisations and the first well designed trial comparing curcumin with PPI for functional dyspepsia, with confirmation through endoscopy and ruling out *H pylori* infection. Limitations of this study included the small number of patients who were lost to follow-up and the lack of long term follow-up data.

Future studies should examine the long term benefits and harms (at least 6–12 months) of curcumin in functional dyspepsia, the use of curcumin on demand in the long term on functional

dyspepsia and the efficacy of curcumin in other functional gastrointestinal disorders.

## Conclusion

Curcumin and omeprazole had comparable efficacy for functional dyspepsia with no obvious synergistic effect.

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**Funding** This study received financial support from the Thai Traditional and Alternative Medicine Fund (Grant No 3-2561).

**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** Consent obtained directly from patient(s).

**Ethics approval** This study involves human participants and was approved by the ethics committee for research in human subjects in the fields of Thai traditional and alternative medicine (TAMEC No 11-2561). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. Data are available from the authors upon reasonable request.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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