

## POTENTIAL BENEFIT OF CURCUMIN ADJUVANT THERAPY TO THE STANDARD *HELICOBACTER PYLORI* ERADICATION THERAPY IN PATIENTS WITH PEPTIC ULCER DISEASE

SHAYMAA HASAN ABBAS<sup>1</sup>, MANAL KHALID ABDULRIDHA<sup>1\*</sup>, AKRAM AJEEL NAJEB<sup>2</sup>

<sup>1</sup>Department of Clinical Pharmacy, College of Pharmacy, Al-Mustansiriya University, Iraq. <sup>2</sup>Consultant Gastroenterologist, Baghdad Teaching Hospital, Medical city, Iraq. Email: pharm.mrdha@uomustansiriyah.edu.iq

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### ABSTRACT

**Objective:** This study was designed to explore the benefit of curcumin as adjuvant therapy to the standard *Helicobacter pylori* eradication triple therapy in both duodenal and gastric ulcers patients.

**Methods:** The present study enrolled 40 patients newly diagnosed endoscopically with peptic ulcer disease to be allocated into group 1 treated with standard *H. pylori* eradication triple therapy, and group 2 patients treated with curcumin (500 mg) capsules three times daily for 14 days as an adjuvant to standard triple therapy. Stool antigen test, immunoglobulin M serology test, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin 1 beta (IL-1 $\beta$ ), and total antioxidant capacity (T-AOC) are measured at the baseline and after 6 weeks of treatment.

**Results:** The result showed that the use of curcumin as adjuvant therapy produced highly significant improvement in healing efficacy which was significantly distinguished in duodenal ulcer patients compared to gastric ulcer groups 2 patients ( $p < 0.05$ ), along with a highly significant reduction in pro-inflammatory IL-1 $\beta$  level in group 2 patients ( $p < 0.01$ ). After 6 weeks of treatment, there was a highly significant elevation in the level of TNF- $\alpha$  in groups 1 ( $p < 0.01$ ), though group 2 patients presented with non-significant elevation in TNF- $\alpha$  level. Moreover, the T-AOC was improved with curcumin adjuvant therapy, though non-significant, compared to group 1 patients who showed a reduction in T-AOC.

**Conclusion:** This study revealed that addition of curcumin as adjuvant therapy produced improvement in ulcer healing efficacy, and controlled the inflammatory and oxidative stress process induced by *H. pylori* infection.

**Keywords:** Peptic ulcer disease, Curcumin, *Helicobacter pylori* infection, Inflammation, Oxidation markers.

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### INTRODUCTION

Peptic ulcer disease (PUD) is the erosion in lining of stomach or duodenum [1]. Predominantly caused by *Helicobacter pylori* infection in about 50% of the world's population [2], which can colonize in the gastric antrum of all patients producing an extensive, non-invasive inflammatory reaction in the gastric mucosa [3]. It stimulates overexpression of pro-inflammatory cytokines (e.g., tumor necrosis factor [TNF- $\alpha$ ] and interleukin [IL-1 $\beta$ , IL-6, and IL-8]) in gastric epithelial cells, which activate neutrophil and lead to leukocyte infiltration [4]. There is an increasing difficulties in the conventional *H. pylori* eradication triple therapy mostly due to antimicrobial resistance [5], which were replaced with many other *H. pylori* eradication protocols [6]. Experimentally, a combination of standard anti-ulcer drugs and herbal medicines displayed a synergistic effect against gastric ulcer and could be used as alternative perspectives in treating certain gastric ulcers and preventing recurrence [7]. Curcumin is the main natural polyphenol present in the rhizome of *Curcuma longa* [8]. It is a lipophilic polyphenol which is nearly insoluble in water, but quite stable in acidic pH of the stomach [9]. It has poor bioavailability and selectivity [10]. Curcumin is widely used in herbal medicine because it possesses many pharmacological properties [11]. Moreover, as a monotherapy, it exhibits remarkable anti-inflammatory, antioxidant, antimicrobial, and anticarcinogenic effect [12]. Besides it display antiulcer activity by attenuating different ulcerative effectors including gastric acid hypersecretion, myeloperoxidase activity, apoptotic incidence, total peroxides, and IL-6, along with its inhibitory activity for pepsin [13]. Several properties help to recognize its anti-*H. pylori* effect, including pro-apoptotic effect, inhibition of angiogenesis, proliferation, and metastasis [14]. Accordingly, this study was designed to explore the benefit of curcumin as adjuvant therapy to the standard *H. pylori*

eradication triple therapy in increasing the healing efficacy, changes in inflammatory markers, improving total antioxidant capacity (T-AOC) of both duodenal and gastric ulcers patients.

### MATERIAL AND METHODS

#### Study design

The present study is a prospective randomized controlled interventional open-label study designed to track the potential effect of curcumin adjuvant therapy in PUD patients.

#### Patients

Forty patients newly diagnosed with PUD (26 females and 14 males) with age ranges between 17 and 70 years, attended the endoscopy unit were enrolled in the study after signing a written consent with ethical approval released by the institution scientific committee. The eligible patients were allocated into group 1 include (19) treated with standard *H. pylori* eradication triple therapy (clarithromycin [500 mg] tablets [Limassol, Cyprus] + amoxicillin [1 g] capsules [Bristol, UK] + esomeprazole [20 mg] tablets [Astrazeneca, Sweden]) all to be given twice daily for 14 days duration, which represent the control group, and group 2 include (21) patients treated with curcumin (500 mg) capsules three times daily for 14 days as adjuvant with the standard *H. pylori* eradication triple therapy, which represents the interventional group.

#### Methods

##### Measurement of *H. pylori*

The *H. pylori* antigen rapid test device (feces) (ABON, China) and *H. pylori* immunoglobulin M antibody ELISA Kit (Cal biotech, USA) are used for *H. pylori* detection in group 1 and group 2 patients at the baseline and after 6 weeks treatment.

### Measurement of serum TNF- $\alpha$

It was determined using commercial enzyme-linked immunosorbent assay (ELISA) kit (Elabscience Biotechnology, China), measured in group 1 and group 2 patients at the baseline and after 6 weeks treatment.

### Measurement of serum IL-1 $\beta$

It was determined using commercial ELISA kit (Elabscience Biotechnology, China), measured in group 1 and group 2 patients at the baseline and after 6 weeks treatment.

### Measurement of serum T-AOC

It was determined using commercial ELISA kit (Qayee-Bio, China), measured in group 1 and group 2 patients at the baseline and after 6 weeks treatment.

### Statistical analysis

The statistical analysis system-Minitab 16.1 (2010) was used to see the effect of different factors on the study parameters. Least significant difference test was used to significantly compare between study parameters, where data expressed as (mean $\pm$ standard deviation) with ( $p>0.05$ ) to be considered not significant, ( $*p<0.05$ ) to be considered as significant, and ( $**p<0.01$ ) to be considered as highly significant. Paired t-test was used to compare between pre- and post-treatment results and the two-sample t-test is used to compare pre- or post-treatment between group 1 and group 2.

## RESULTS

### Demographic data and disease characteristics of patients with PUD

The study groups are allocated into group 1 (19 patients) which represents the comparative control, and group 2 (21 patients) which represents the intervention group (Table 1). The mean age of peptic ulcer patients in group 1 was 41.16 $\pm$ 12.26 years, and the mean age of patients in group 2 was 44.09 $\pm$ 15.43 years. The mean body mass index (BMI) of group 1 patients was 27.57 $\pm$ 5.89 kg/m<sup>2</sup>, and for group 2 patients was 26.66 $\pm$ 4.28 kg/m<sup>2</sup>. Group 1 include (63.16%) female and (36.84%) male genders, while group 2 include (66.67%) female and (33.33%) male. Peptic ulcer patients represented (63.18%) as duodenal ulcer and 52.63% as gastric ulcer in group 1, and 61.90% as duodenal ulcer and 47.61% as gastric ulcer in group 2. Positive family history was seen in 10.5% of patients in group 1 and 9.52% in group 2. There was no statistically significant difference in the mean values of age, BMI, gender, type of peptic disease and family history between both study group patients ( $p>0.05$ ). The duration of symptoms of less than 1 years was 78.95%, and between 1 and 5 years was 21.05% in group 1 patients. While in group 2 patients the duration of symptoms of less than 1 year was 52.38%, and between 1 and 5 years was 47.62%. There was no patient presented with symptoms exceeding (5) years. The statistically significant difference was found in the duration of symptoms of <1 years ( $p<0.05$ ) and highly significant difference in duration of symptoms of (1-5) years ( $p<0.01$ ) between both groups. The smoking habit was positive in 15.79% of group 1 patients and 14.29% of group 2 with no statistical difference between both groups ( $p>0.05$ ).

### Effect of *H. pylori* eradication triple therapy alone and in combination with curcumin on healing efficacy after 6 weeks of treatment

Group 1 peptic ulcer patients presented with (57.89%) of healing efficacy after *H. pylori* eradication with standard triple therapy, while the mean percentage of healing efficacy of standard triple therapy in combination with curcumin in group 2 peptic ulcer patients was (89.47%) after 6 weeks of treatment. Statistically high significant difference in healing efficacy was found among both study groups 1 and 2 patients ( $p<0.01$ ) after 6 weeks up ceiling for group 2 patients on curcumin adjuvant therapy (Table 2). According to the location of ulcer, there was a statistically significant increase in the percentage of ulcer healing efficacy of *H. pylori* in groups 2 duodenal ulcer patients

compared to groups 1 patients ( $p<0.05$ ) after 6 weeks of treatment, with no significant difference in respect to gastric ulcer patients.

### Effect of *H. pylori* eradication triple therapy alone and in combination with curcumin on inflammatory markers in peptic ulcer patients after 6 weeks of treatment

In the present study, there was no statistically significant difference at the baseline level of TNF- $\alpha$  between both study groups 1 and 2 ( $p>0.05$ ). After 6 weeks of treatment, there was highly significant increase in the level of TNF- $\alpha$  in groups 1 ( $p<0.01$ ), but in group 2 patients, the increase in TNF- $\alpha$  level presented was non-significant after 6 weeks of treatment compared to the pretreatment level ( $p>0.05$ ) (Table 3). Moreover, there was no statistically significant difference at the baseline level of IL-1 $\beta$  between both study groups 1 and 2 ( $p>0.05$ ). After 6 weeks of treatment, results of group 2 patients showed highly significant decrease in the level of IL-1 $\beta$  compared to pretreatment level ( $p<0.01$ ), while group 1 patients presented with no significant decrease in IL-1 $\beta$  level ( $p>0.05$ ).

### Effect of *H. pylori* eradication triple therapy alone and in combination with curcumin on T-AOC in peptic ulcer patients after 6 weeks of treatment

There was no significant difference at the baseline level of mean T-AOC between both study groups 1 and 2 ( $p>0.05$ ). However, after 6 weeks of treatment there was an increase in the level of mean T-AOC in study groups 2 patients, though non-significant, patients in study group 1 showed a reduction in the level of mean T-AOC compared to pretreatment level ( $p>0.05$ ) (Table 4).

## DISCUSSION

The *H. pylori* infection is a worldwide problem in patients with PUD with a high rate of morbidity and mortality [15,16]. Several studies were conducted to evaluate the most effective therapeutic regimen for improving the eradication rate of *H. pylori* infection and obtaining higher healing efficacy [17-21]. This study is another attempt in this respect, though at a smaller scale, which might be (at least to best knowledge) the first attempt to evaluate the efficacy of curcumin as an adjuvant to the standard triple *H. pylori* eradication therapy.

**Table 1: Demographic data and disease characteristics of patients with peptic ulcer disease**

Variable	Study groups		
	Group 1 (n=19)	Group 2 (n=21)	p value
Age (years)	41.16 $\pm$ 12.26	44.09 $\pm$ 15.43	0.751 <sup>NS</sup>
Range (years)	20-63	17-70	
BMI kg/m <sup>2</sup>	27.57 $\pm$ 5.89	26.66 $\pm$ 4.28	0.902 <sup>NS</sup>
Gender			
Female	12 (63.16)	14 (66.67)	0.751 <sup>NS</sup>
Male	7 (36.84)	7 (33.33)	0.679 <sup>NS</sup>
Total	19 (100)	21 (100)	
Type of PUD			
Duodenal ulcer	12 (63.18)	13 (61.90)	0.909 <sup>NS</sup>
Gastric ulcer	10 (52.63)	10 (47.61)	0.616 <sup>NS</sup>
Family history			
Positive	2 (10.5)	2 (9.52)	0.827 <sup>NS</sup>
Negative	17 (89.47)	19 (90.48)	0.940 <sup>NS</sup>
Duration of symptoms (years)			
<1	15 (78.95)	11 (52.38)	0.02*
1-5	4 (21.05)	10 (47.62)	0.001**
>5	-	-	
Smoking habit			
Positive	3 (15.79)	3 (14.29)	0.784 <sup>NS</sup>
Negative	16 (84.21)	18 (85.7)	0.909 <sup>NS</sup>

Data presented as mean $\pm$ SD; (n) is number of patients and (%) is a percentage. Chi-square test for numerical values to compare between group 1 and group 2 where; NS: Not significant ( $p>0.05$ ); \* ( $p<0.05$ ) is considered significant; \*\* ( $p<0.01$ ) is considered highly significant. BMI: Body mass index, PUD: Peptic ulcer disease, SD: Standard deviation

**Table 2: Effect of *H. pylori* eradication triple therapy alone and in combination with curcumin on healing efficacy after 6 weeks of treatment**

Study groups	Patient (n)	Ulcer healing efficacy n (%)	Ulcer healing efficacy		p value
			DU n (%)	GU n (%)	
Group 1	19	11 of 19 (57.89)	6 of 12 (50.00)	5 of 10 (50.00)	1.00 <sup>NS</sup>
Group 2	21	17 of 21 (89.47)	10 of 13 (76.92)	7 of 10 (70.00)	0.859 <sup>NS</sup>
p value		0.009**	0.017*	0.564 <sup>NS</sup>	

Data presented as; (n) is number of patients and (%) is a percentage. Chi-square test for numerical values to compare between group 1 and group 2 where; NS: Not significant (p>0.05); \*(p<0.05) is considered significant; \*\*(p<0.01) is considered highly significant. *H. pylori*: *Helicobacter pylori*

**Table 3: Effect of *H. pylori* eradication triple therapy alone and in combination with curcumin on inflammatory markers in peptic ulcer patients after 6 weeks of treatment**

Variable	Study groups		
	Group 1 (n=19)	Group 2 (n=21)	p value
TNF-α (pg/ml)			
Pre-treatment	12.78±11.67	22.02±18.87	0.069 <sup>NS</sup>
Post-treatment	27.43±19.60	29.19±20.29	0.782 <sup>NS</sup>
p value	0.004**	0.149 <sup>NS</sup>	
IL-1β (pg/ml)			
Pre-treatment	13.186±11.15	24.69±23.85	0.057 <sup>NS</sup>
Post-treatment	9.12±8.89	7.713±5.7	0.561 <sup>NS</sup>
p value	0.099 <sup>NS</sup>	0.002**	

Data presented as mean±SD. Paired t-test to compare pre and post treatment variables and two sample t-test to compare pre- or post-treatment variables where; NS: Not significant (p>0.05), \*\* (p<0.01) is considered highly significant. SD: Standard deviation, TNF-α: Tumor necrosis factor-alpha, IL-1β: Interleukin 1 beta

**Table 4: Effect of *H. pylori* eradication triple therapy alone and in combination with curcumin on T-AOC in peptic ulcer patients after 6 weeks of treatment**

Variable	Study groups		
	Group 1 (n=19)	Group 2 (n=21)	p value
T-AOC (ng/ml)			
Pre treatment	50.7±45	37.06±12.66	0.216 <sup>NS</sup>
Post treatment	47.63±25.27	40.31±13.24	0.268 <sup>NS</sup>
p value	0.73 <sup>NS</sup>	0.108 <sup>NS</sup>	

Data presented as mean±SD. Paired t-test to compare pre- and post-treatment variables and two sample t-test to compare pre- or post-treatment variables where; NS: Not significant (p>0.05). SD: Standard deviation, *H. pylori*: *Helicobacter pylori*, T-AOC: Total antioxidant capacity

The activity of curcumin alone in PUD was experimentally *in vitro* investigated previously as possessing antioxidant and anti-inflammatory properties, and to attenuating gastric hypersecretion (as a major pathology caused by *H. pylori* microorganism in gastric and duodenal ulcer) [13]. In addition, apoptotic and myeloperoxidase activity, along with its inhibitory effect for pepsin was found [13]. Moreover, several other *in vivo* and *in vitro* studies explored the inhibitory effect of curcumin against *H. pylori* growth, consequently eradicate *H. pylori* infection [22-24]. In clinical trials, curcumin supplement alone is still under investigation in which it is expected to play a potential role in suppressing *H. pylori* growth, and may promote healing of peptic ulcers [25,26].

In the present study, and in many others, patients with PUD caused by *H. pylori* infection were mostly in a middle age of <50 years [27-30]. Female patients had the higher rate of infection with *H. pylori* microorganism, similar finding was found among Iraqi population in other studies [31,32], inversely, male gender was predominant to females in others [33,34]. Higher percentage of peptic ulcer patients diagnosed endoscopically as duodenal ulcer compared to these with gastric ulcer in the present study. This finding was in agreement with

previous cohort study on PUD patients [35]. Comparable results showed that patients with duodenal ulcers had a higher rate of *H. pylori* infection [36,37].

Positive family history and smoking habits were correlated positively with the incidence of PUD in a previous study [38]. The *H. pylori* infections tend to distributed within families by close person-to-person contact [39], hence, *H. pylori* infection has a high risk to develop gastroduodenal diseases in individuals with positive family history [40]. Other data reported by Shokrzadeh *et al.* showed that positive family history of PUD was seen in about 24% of *H. pylori* positive patients [40]. Furthermore, the present study reported statistically significant difference in duration of symptoms <1 years and high significant difference in duration of symptoms 1-5 years between both study groups 1 and 2, while there were no patients presented with symptoms exceeding 5 years.

Recalling that curcumin possess inhibiting effect on gastric acid secretion, inhibiting the activity of pepsin, and reducing juice acidity [13]. Furthermore, it poses inhibiting effect against NFκB activation and macromolecular leakage induced by *H. pylori* infection; all would explain ulcer healing property of curcumin [26].

In the present study, the healing efficacy of peptic ulcer was increased from (57.89%) with slandered triple therapy alone up to (89.47%) after addition of curcumin adjuvant therapy. The therapeutic potential of curcumin as a monotherapy against *H. pylori* infection was elegantly studied and reviewed previously by many researchers [5,22,41,42], meanwhile Di Mario *et al.* stated that administration of 7 days curcumin 30 mg b.i.d, bovine lactoferrin 100 mg b.i.d, N-acetylcysteine 600 mg b.i.d, and pantoprazole 20 mg b.i.d produce only (12%) cure of dyspeptic patients infected with *H. pylori*, nevertheless, a significant reduction in severity of overall symptoms after 2 months was noticed [43].

With reference to the global trend of *H. pylori* eradication therapy which has now shifted towards proton pump inhibitor (PPI)-based triple therapy (a PPI and different antimicrobials) [6], which was studied extensively on Iraqi group of patients as well [21,44] can assure rapid symptom relief, reduce ulcer recurrence, and improve ulcer healing. However, many bacterial and host factors are contribute to the failure of *H. pylori* eradication, especially factors affecting PPI bioavailability and metabolism [45,46], besides the low patient compliance, especially in elderly patients [47,48]. In the last decades, the increasing incidence of clarithromycin-resistant strains of *H. pylori* became the most important cause for treatment failure [46,49]. Taken together all these facts, this study might be a new trend towards improving *H. pylori* eradication rate with the addition of curcumin to the (PPI)-based triple therapy, which alone revealed a (42.1%) eradication failure rate.

The current study explored that the addition of curcumin to the standard *H. pylori* triple therapy produce a significant increase in ulcer healing efficacy in both patient groups with up ceiling effect in duodenal ulcers (76.92% vs70%) when compared with standard *H. pylori* eradication triple therapy. These results were in agreement with that of Purcksunand *et al.* who found that healing efficacy after curcumin as a mono-treatment for 3 months was (73%) in patients with duodenal ulcer and (27%) in patients with gastric ulcer in phase II clinical

trial [26]. The predominant colonization of *H. pylori* in the duodenal region [50], along with the inhibitory effect of curcumin against *H. pylori* growth and attenuating gastric hypersecretion (as a major pathology caused by *H. pylori* microorganism in gastric and duodenal ulcer) as mentioned earlier, this would make acceptable explanation for the incremental healing efficacy in duodenal ulcers.

The key physiological event in *H. pylori* infection is the induction of inflammatory response in the gastric mucosa. This microorganism stimulates transcription and synthesis of many inflammatory cytokines especially IL-1 $\beta$  and TNF- $\alpha$  [51]. The effect of curcumin on the inflammatory markers induced by *H. pylori* infection in peptic ulcer patients is still under investigation, several studies were conducted to explore the anti-inflammatory effect of curcumin as a monotherapy [52-54].

In the present study, the addition of curcumin to the standard triple *H. pylori* eradication therapy produce some suppressive effect against the up ceiling rise in the TNF- $\alpha$  level which was noticed significantly in patients on standard *H. pylori* triple therapy alone, giving some promising protective effect to the gastric and duodenal mucosa against *H. pylori* virulence.

Moreover, in the present study, curcumin adjuvant therapy produced highly significant reduction ( $p < 0.01$ ) in mean IL-1 $\beta$  level (another pro-inflammatory mediator) in comparison with patients treated with standard *H. pylori* triple therapy alone after 6 weeks treatment. No matched interventional study was available to precisely interpret these results, though, it can be said that curcumin might produce synergistic anti-inflammatory effect which cannot be obtained when using standard *H. pylori* triple therapy alone.

The inhibitory effect of curcumin monotherapy on IL-1 $\beta$  and TNF- $\alpha$  production in ulcerated gastric mucosa caused by *H. pylori* infection was documented experimentally [23,24,26,55] and was detected in the human study [56], with some controversy [42]. Kundu *et al.* suggested that curcumin act by two ways against *H. pylori* infection; first as antibacterial via eradicating *H. pylori* infection, and second; potentially targeting key molecules involved in the *H. pylori* -induced gastric diseases [23]. In addition, Di Mario *et al.* found that treatment with curcumin significantly reduces the serologic signs of gastric inflammation associated with *H. pylori* infection despite the persistence of the bacterium [43]. Curcumin can also prevent indomethacin-induced gastropathy by improvement the gastric microcirculation through attenuating the level of intercellular adhesion molecule (ICAM)-1 and TNF $\alpha$  levels compared to treatment with indomethacin alone [57]. IL-1 genetic polymorphisms influenced *H. pylori*-related gastric mucosal IL-1 $\beta$  levels which may lead to gastric inflammation and atrophy; factors thought to be important in gastric carcinogenesis [58], it can be speculated that curcumin potentially plays a role in this aspect.

Oxidative stress may represent an important mechanism leading to epithelial injury in *H. pylori* infection [59], characterized by an increase in the reactive oxygen species levels in the infected patient's mucosa [60]. There was statistically incremental elevation, though non-significant, in the level of T-AOC in the present study after 6 weeks of treatment with curcumin adjuvant therapy, and a decrease in T-AOC with standard *H. pylori* triple therapy alone. *In vitro* study, Tuba *et al.* found that ethanolic extract of *C. longa* leaves had the ability to attenuate the free radical mediated lipid peroxidation and scavenged free radical [61]. The anti-oxidant and free radical scavenging effects of curcumin counteracted with reactive oxygen and nitrogen species thereby protected cells from oxidative damage [62]. Experimentally, Abdul-Aziz found a significant increase in TAO-C level in serum and gastric juice after treatment with curcumin alone for a stomach ulcer in Shay rat model [63], and the level of total peroxides was significantly reduced in serum and gastric juice of curcumin treated rats [63].

## CONCLUSION

This study revealed that addition of curcumin as an adjuvant to standard triple *H. pylori* eradication therapy produced improvement in ulcer healing efficacy in peptic ulcer patients, and controlled the inflammatory and oxidative stress process induced by *H. pylori* infection, allowing to speculate the promising therapeutic effect of curcumin as an adjuvant therapy.

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