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Possible Antibacterial Activity of Curcumin and Mangiferin in Patients with *Helicobacter pylori* –Associated Functional Dyspepsia

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Abstract

Background and objectives: Since the introduction to the scientific community by Marshall and Warren in 1982, the gram-negative bacterium *Helicobacter pylori* (*H. pylori* or HP), is now recognized as the primary causative agent associated with the development of gastritis and peptic ulcer disease. The effectiveness of many of the frequently recommended antibiotic-based *H. pylori* eradication regimens has been increasingly compromised by antimicrobial resistance and the higher incidence of adverse effects. Some *in vitro* studies have shown the effectiveness of curcumin and mangiferin against Helicobacter pylori. The aim of this study is to test the efficacy of curcumin and mangiferin as components of dual or triple proton pump inhibitor-based *H. pylori* eradication regimens in patients with *H. pylori*-associated functional dyspepsia.

Methods: *H. pylori* status was tested using the non-invasive stool antigen test before and 4 weeks after eradication therapy.

Results: Following 14-day therapy, significantly higher eradication rates were obtained with triple curcumin/mangiferin/omeprazole regimen compared to dual curcumin/omeprazole and dual mangiferin/omeprazole regimens (90% versus 60% and 50%, $p \leq 0.05$). All eradication regimens dramatically reduced dyspeptic symptoms and were well tolerated with negligible side effects.

Conclusions: Curcumin and mangiferin preparations traditionally used for the treatment of gastrointestinal disorders are effective as components of *H. pylori* eradication regimens with little or no adverse reactions.

Keywords: *Helicobacter pylori*; Curcumin; Mangiferin; Omeprazole; Functional dyspepsia

Abbreviations: GI: Gastrointestinal; MALT: Mucosa-Associated Lymphoid Tissue; GORD: Gastro-Oesophageal Reflux Disease; IBS: Irritable Bowel Syndrome; HpSA: *Helicobacter Pylori* Stool Antigen; ADRs: Adverse Drug Reactions

Introduction

Helicobacter pylori (*H.pylori*) is a gastric Gram-negative, spiral-shaped microaerophilic pathogen closely associated with gastric and extra-gastric diseases Hu et al. [1]. Appropriately half of the global population is infected with *H. pylori*, and the prevalence of *H. pylori* varied among regions, which appeared to be explained by the differences in economic and social conditions Hooi & Zamani et al. [2,3]. It is now widely accepted that *H.pylori* is the etiological agent in numerous gastrointestinal (GI) disorders, including dyspepsia, duodenal and gastric ulcer, gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma Laheij & Chunder et al. [1,4,5]. Following colonization of the gastric mucosa, *H. pylori* induce an inflammatory reaction with neutrophilic gastritis that ultimately results in the clinical manifestation of the infection Go & Crowe [6]. Currently, there several methods for detecting the presence of HP infection, some are invasive (i.e. require endoscopic biopsy) and others are non-invasive. Histologic evaluation El-Zimaity & Graham [7], culture Perez-Perez [8], polymerase chain reaction Bravos & Gilman [9], and rapid urease tests Midolo & Marshall [10] are typically performed on tissue obtained at endoscopy. Simple non-invasive tests include urea breath tests Vaira & Vakil [11], serology Cutler et al. [12], and stool antigen testing Monteiro et al. [13]. A review of 22 studies showed that HP stool antigen test had a pretreatment sensitivity of 94% and specificity of 97% and a post treatment sensitivity of 93% and specificity of 96% Gisbert & Gisbert et al. [14,15]. Determining the optimum treatment of HP infection is difficult because the organism lives in an environment not easily accessible to many medications and because emerging bacterial resistance presents an added challenge. The choice of therapy should consider effectiveness, cost of various regimens and

side effects. Conventional HP treatment involves multiple drug short-course regimens of antisecretory agents and antibiotics. Despite effective eradication therapies, permanent cure is not always possible where re-infection from environmental sources is highly common Sullivan et al. [16]. Due to the high level of adverse effects associated with the antimicrobials commonly employed in the eradication of HP and the increasing incidence of antimicrobial resistance, much interest has been generated in the development of newer HP eradication modalities. Herbal medicines have been used traditionally for the treatment of a wide range of gastrointestinal disorders including dyspepsia, gastritis and peptic ulcer disease Borrelli & Thompson [17,18].

Curcumin is a key hydrophobic polyphenolic yellow pigment isolated from turmeric rhizome Curcuma longa Linn, Cai et al. [19]. Turmeric mainly contains three curcuminoids (curcumin, demethocycurcumin, and bisdemethoxycurcumin) and volatile oil Basnet & Hamidpour et al. [20,21]. Curcumin has anti-oxidant, anti-inflammatory, anticarcinogenic and anti-microbial properties Anand & Cai et al. [19,22]. Moreover Chemotherapeutic, chemo-preventive Sharma et al, [23], hepatoprotective, nephro-protective, thrombosis suppressing, hypoglycemic and anti-rheumatic effects of curcumin are also well-established Anand et al. [22]. Studies showed that curcumin can cause a high rate of *H. pylori* eradication and gastroprotective effects in mice De et al. [24]. *In vitro* studies have shown the effectiveness of curcumin extracts against *H. pylori* De et al. [24], Sarkar et al. [25], Vetvicka et al. [26], Ranjbar & Mohammadi [27].

Mangiferin is a polyphenol (xanthonoid) commonly found in the bark, fruits, and leaves of *Mangiferin indica* L and in the roots of *Salacia chinensis* Lv et al. [28]. Mangiferin has a broad spectrum of pharmaceutical activities such as antioxidant, anti-inflammation, anti-microbial, anti-invasive, anti-tumor Wauthoz, Singh & Anand et al. [29-31]. Enormous studies had indicated that mangiferin might act as an anti-carcinogen in various cancer cell line model attributing to its antioxidant, anti-inflammatory, anti-proliferative (cytotoxic), anti-adhesive, and pro-poptotic effect du Plessis-Stoman & Rajendran et al. [32,33]. Moreover, the gastroprotective activity of mangiferin was reported in an animal model Carvalho et al. [34]. *In vitro* studies have shown the effectiveness of mangiferin extracts against many bacteria including *H. pylori* Doughari, Sanrawal & Zhang [35-37].

In this work, curcumin and mangiferin preparations were assessed clinically for their HP-eradicating efficacy as components of dual or triple omeprazole-based regimens in patients with functional dyspepsia.

Patients and Methods

Study design

Sixty *H.pylori*-positive patients (48 men, 12 women) aged 20 to 56 years with functional dyspepsia, were enrolled in this randomized open-label efficacy study. The study protocol was approved by the Ethics Committee at Al-Amal Specialized Hospital, Cairo, Egypt. Signed written informed consents were obtained from all patients participating in the study. All patients were subjected to detailed history taking (stressing the onset and duration of dyspepstic symptoms), clinical examination and routine laboratory investigations. Functional (non-ulcer) dyspepsia was diagnosed according to the Rome III criteria for functional gastrointestinal disorders Chunder [5]. Patients were randomized to 3 groups, 20 patient each. The first group received Curcumin (400 mg capsule twice daily) plus omeprazole (20 mg twice daily). The second group was treated with mangiferin (200 mg capsule mg capsule twice daily) plus omeprazole (20 mg twice daily). The third group received a combination of curcumin (400 mg capsule twice daily), mangiferin (200 mg capsule twice daily) and omeprazole (20 mg twice daily). All treatments were given for 14 days. *H. Pylori* status was determined by the non-invasive stool antigen test Vaira & Vaira et al. [38,39], before and 4 weeks after eradication therapy Burette [40]. To ensure better patient adherence, the study medications were refilled freely on a weekly basis. During the treatment period, patient education, counselling and clinic visits were planned weekly. Symptom review, medication use and adverse reactions were recorded in each visit.

Setting

Out-patient treatment at Al-Amal Specialized Hospital Internal Medicine Clinic, Cairo, Egypt.

Inclusion criteria

Helicobacter pylori-positive dyspeptic patients fulfilling the Rome III diagnostic criteria for functional dyspepsia. According to Rome III criteria, functional dyspepsia is diagnosed when; one or more of the following symptoms are present for at least three months, with onset occurring at least six months before: a) early satiation; b) bothersome postprandial fullness; c) epigastric burning; d) epigastric pain; and e) no evidence of structural disease that is likely to explain the symptoms.

Exclusion criteria

Patients with history of peptic ulcer disease, gastro-oesophageal reflux disease (GORD) or irritable bowel syndrome (IBS), previous treatment with proton pump inhibitors in the preceding 2 weeks of eradication therapy or previous treatment with any antimicrobial agent in the preceding 4 weeks of eradication therapy.

Study drugs

Curcumin 400 mg capsules (contains 100mg curcuminoids), Pharma Nord, (UK) Ltd.

Mangiferin 200 mg capsules (Mango leaf extract containing ~ 60% mangiferin), Green Dragon Botanicals, Brattleboro, Vermont, USA.

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Omeprazole 20 mg (Losec®), AstraZeneca.

Helicobacter pylori testing

Helicobacter pylori status was tested before and 4 weeks after eradication therapy using *Helicobacter Pylori* Stool Antigen (HpSA), Test Kit, Code # 53850, Focus Diagnostics, Cypress, California 90630 USA. The principle of the test depends on an immunochromatographic assay that uses antibody- coated colloidal gold to detect the presence of *H. pylori* antigens in stool specimens. The test detects directly antigens in specimens for an active infection. The test is simple and easy to perform and the test results can be visually interpreted within 15 minutes.

Patient education

Patient education and counselling was performed at the start and on weekly-basis throughout the study. Patients were educated and reassured on the meaning of the symptoms and their benign nature and encouraged to take responsibility for their own health care. Patients were advised of the following lifestyle and dietary modifications:

a) Avoid high-fat meals, alcohol and caffeinated drinks.

b) Eat frequent, but smaller meals, throughout the day and avoid late evening meals

c) Smoking cessation and weight reduction

d) Adopt relaxation and stress management techniques

e) Avoid foods that trigger or worsen the dyspeptic symptoms such as onions, coffee, peppers, citrus fruits, spices and carbonated beverages.

f) Review of current medication for possible cause of dyspepsia.

Efficacy measures

Primary efficacy measures depend on finding out HP-eradication rates (%) observed for each therapeutic regimen following 14-day therapy using *Helicobacter Pylori* Stool Antigen (HpSA), Test. Secondary efficacy measures involve monitoring improvements in the severity and frequency of dyspeptic symptoms.

Safety measures

Safety was assessed by monitoring the incidence of adverse drug reactions (ADRs) and clinical examination. Clinical examination and ADRs were evaluated at weekly intervals.

Data analysis

Helicobacter pylori eradication rates (%) were compared using Fisher's exact test (Joosse SA., 2011, available from http://in-silico.net/statistics/fisher_exact_test). The level of significance was set at $p \leq 0.05$.

Results

Efficacy measures

The *H. pylori* eradication rates following 14-day therapy were 60% with mangiferin plus omeprazole, 70% with curcumin plus omeprazole and 90% when both curcumin and mangiferin were used in combination with omeprazole. Results are presented in Table 1. As shown in Figure 1, significantly higher eradication rates were obtained with triple curcumin/mangiferin/omeprazole regimen compared to dual curcumin/omeprazole and dual mangiferin/omeprazole regimens (90% versus 60% and 50%, Fisher's exact test, $p \leq 0.05$). The severity, duration and frequency of dyspeptic symptoms were dramatically reduced within hours following initiation of therapy, especially with the triple eradication regimen.

Table 1: *H pylori* eradication rates with three different herbal omprazole-based regimens.

Regimen	No of Patients	*H. pylori* Eradication Rates (%)
Mangiferin/Omeprazole	20	50
Curcumin/Omeprazole	20	60
Curcumin/Mangiferin/Omeprazole	20	90*

Helicobacter pylori eradication rates following 14-day treatment with three different omeprazole-based regimens.*Significantly different from dual regimens ($p \leq 0.05$, Fisher's exact test).

Safety measures

All eradication regimens were well tolerated with slight side effects. The most common side effects observed were nausea, fatigue and headache; all are of mild transient nature.

Discussion

Helicobacter pylori has been associated with the pathogenesis of antral gastritis, duodenal ulcer, and gastric lymphoma. Eradication of *H. pylori* has been shown to reverse or prevent relapse of these diseases. Conventional *H. pylori* treatment involves multiple drug short-course therapy. Gastric acid supressants such as ranitidine or omeprazole have in-vitro activity against HP De Boer et al. [41]. A proton pump inhibitor (e.g., omeprazole) plus clarithromycin plus either amoxicillin or metronidazole have demonstrated impressive eradication rates (> 85%) when used for 10-14 days Chey & Stenström et al. [42,43]. However, antimicrobials employed in the eradication of *H. pylori* are not without adverse effects and have growing rates of microbial resistance Rimbara & Savoldi et al. [44,45], therefore, newer treatment modalities are required.

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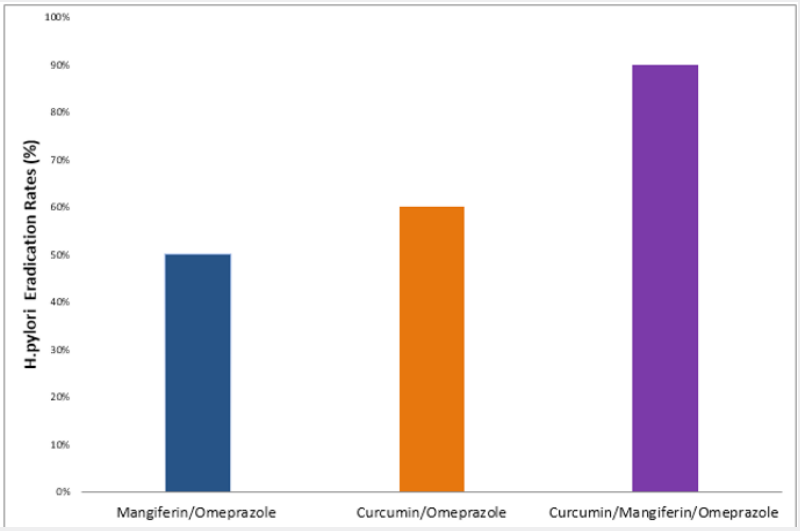

Figure 1: Helicobacter pylori eradication rates following 14-day treatment with three different omeprazole-based regimens. *Significantly different from dual regimens ($p \leq 0.05$, Fisher's exact test).

The results of the present study revealed that triple curcumin/mangiferin/omeprazole regimen achieved significantly higher *H. pylori* eradication rates compared to dual curcumin/omeprazole and dual mangiferin/omeprazole regimens in patients with *H. pylori*-associated functional dyspepsia. The *H. pylori* eradication rate observed with the triple curcumin/mangiferin/omeprazole regimen is comparable to that reported with the conventional anti-*H. pylori* regimen consisting of omeprazole/clarithromycin plus either amoxicillin or metronidazole. All regimens reduced the severity, duration and frequency of dyspeptic symptoms within few hours following initiation of therapy. The eradication regimens were well tolerated with negligible side effects. The most common side effects observed were nausea, fatigue and headache; all are of mild transient nature. One of the positive outcomes of the study is that the level of patient awareness with their illness was increased as compared to that preceding the study.

Many herbal medicines including curcumin and mangiferin have been used universally as folklore remedies for gastrointestinal disorders. Mangiferin and mango leaves afford gastro protection against gastric injury through the antisecretory and antioxidant mechanisms of action Carvalho & Neelima et al. [34,46]. Studies suggest that curcumin has a wide range of beneficial properties in many GIT diseases including oral cancer and cancer of the submandibular gland Rai et al. [47], esophageal cancer Hartojo et al. [48] gastric cancer Koo et al. [49], colon cancer Johnson & Mukhtar [50], inflammatory bowel disease Holt et al. [51], pancreatic cancer Swamy et al. [52], hepatocellular carcinoma Lin et al. [53] and liver fibrosis.

In vitro studies have shown the effectiveness of curcumin extracts against *H.pylori* De et al. [24], Sarkar et al. [25], Vetvicka et al. [26], Ranjbar & Mohammadi [27]. All previous studies on curcumin have indicated its bacterial membrane altering properties such as thinning and disruption of the membrane at high concentrations using artificial membranes Anand et al. [54]. Curcumin's anti-*H.pylori* activity can be attributed to bacterial membrane permeabilizing damage that allows for combined antibiotics to be taken up easily through disrupted bacterial membranes Tyagi et al. [55]. Because of participation of free radicals in the pathogenesis of Helicobacter infection, eliminating these causal inflammatory triggers by the use of curcumin may be a useful strategy. Curcumin can decrease lipid peroxidation (an oxidative damage index) and myeloperoxidase activity through its potent antioxidant activity Menon & Sudheer [56]. Kali et al, [57] reported that curcumin had an inhibitory effect on biofilm-producing bacteria when used with antibiotics. They also stated that the use of this substance would be beneficial in antibiotic therapy Kali et al. [57]. The results of our study were also in line with the above studies.

In vitro studies have shown the effectiveness of mangiferin extracts against many bacteria including *H.pylori* Doughari, Sanrawal & Zhang [35-37]. Vaghasiya et al, [58], reported that ethanolic mango extract containing mangiferin showed potent antibacterial activity against all the clinically isolated bacterial strains and most of the standard bacterial strains which was comparable with that of standard antibiotics Vaghasiya et al, [58]. The anti-*H.pylori* activity of mangiferin may be related to its antoxidant Agarwala & Sellamuthu et al. [59,60] and anti-inflammatory activity Carvalho & Morais et al. [34,61].

H. pylori is a known source of free radical production in gastroduodenal disorders Smoot & Sezikli et al. [62,63]. By virtue of their antioxidant properties, attenuation of the damaging effects of *H. pylori*-generated free radicals on gastrodudenal mucosa

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may contribute to both curcumin' and mangiferin's beneficial effects in eliminating dysepeptic symptoms. Considering the strong link between dyspepsia and *H. pylori* infections Frigo et al. [64], Laheij et al. [4], inhibition of *H. pylori* by curcumin and mangiferin preparations suggests a plausible mode of action for their therapeutic benefits in dyspepsia and other gastrointestinal disorders [65-69].

Conclusions

In conclusion, the results of this work demonstrate that curcumin and mangiferin preparations traditionally used for the treatment of gastrointestinal disorders are effective as components of proton pump based- *H. pylori* eradication regimens with little or no adverse reactions. Since *H. pylori* is the causative agent responsible for dyspepsia, gastritis, peptic ulcer disease and gastric carcinoma, might provide newer herbal weapons that can be added to the available antibiotic arsenal. These preparations could furnish a potent anti-*H. pylori* alternative therapy that overcomes the problem of resistance associated with current antibiotic treatment. From the pharmacoeconomic point of view, these herbal preparations provide effective low-cost substitutes to the presently used antibiotics.

Conflict of Interest

I declare that there is no conflict of interest on this research work. No funds or support were obtained from any source.

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