PHASE II CLINICAL TRIAL ON EFFECT OF THE LONG TURMERIC (*CURCUMA LONGA* LINN) ON HEALING OF PEPTIC ULCER

Chaweewan Prucksunand[1], Bunjob Indrasukhsri[2], Manit Leethochawalit[3] and Korpong Hungspreugs[4]

[1]Department of Pharmacology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok; [2]Department of Surgery, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok; [3]Division of Gastroenterology, Department of Medicine, Vajira Hospital, Bangkok; [4]Division of Gastroenterology, Department of Medicine, Somdej Prapinklao Hospital, Bangkok, Thailand

Abstract. The study examined patients who had symptoms indicating peptic ulcer. Forty-five patients, 24 males and 21 females, aged between 16-60 years were included in the study. Twenty-five patients, 18 males and 7 females, were endoscoped, their ulcers located in the duodenal bulb and gastric (angulus). The ulcer sizes varied between 0.5 to 1.5 cm in diameter. Capsule-filled turmeric was given orally in the dose of 2 capsules (300 mg each) five times daily, one half to an hour before meals, at 16.00 hours and at bedtime continuously. The result after 4 weeks of treatment showed that ulcers were absent in 48% or 12 cases (DU 9 and GU 3). Eighteen cases (DU 13 and GU 5) had absence of ulcer after 8 weeks of treatment. Nineteen cases (76%) (DU 14 and GU 5) did not have ulcers after 12 weeks of treatment. The rest, 20 cases were not found to have ulcers and some were not endoscoped. They appeared to have erosions, gastritis and dyspepsia. They received turmeric capsules for 4 weeks of treatment. The abdominal pain and discomfort satisfactorily subsided in the first and second week. They could take normal foods instead of soft meals. Blood chemistry and hematology of all 54 patients had no significant changes in hematological system, liver and renal functions both before and after treatment.

INTRODUCTION

Many Thai people suffer from abdominal pain due to gastric and duodenal ulcers. Traditional doctors used pills "Khamin Chan (Turmeric)" powder mixed with honey to successfully cure their ailment. Assawapantanakul (1981, 1990), reported in people such as officers, monks, teachers and students who ate turmeric pills were cured. We were interested in proving the effects of turmeric on epithelial mucosa of stomach and duodenum of peptic ulcer patients, whether the healing of the ulcer in the mucosa by endosopy corresponds to the disappearance of abdominal pain.

Turmeric is a herb-containing rhizome, which has an orange yellow color, characteristic odor and a bitter taste. This herb is propagated vegetatively through the rhizome. It is easily grown in the rainy season conditions of May to July. In winter and summer the plant leaves disappear. The rhizome remains underground. In the rainy season the plant sprouts and grows again. The crop is ready for harvest in 7 to 9 months after planting and the main harvest season begins from December and extends to February. Turmeric grows throughout Southeast Asia, *eg* Thailand, Lao PDR, Cambodia and India.

Turmeric has been a household plant and is used in several traditional folklore prescriptions, as well as over the counter (OTC) drugs since ancient times (Assawapantanakul, 1981, 1990; Tontiwat, 1978; Pecharaply, 1997; Koy-sooko *et al*, 1993; Pongbunroad, 1965; Bunyapraphatsara, 1986). For example, the rhizome is used orally for regulation of health. It has a choleretic action, causing increased flow of bile into the intestine and is a remedy for dyspepsia and diarrhea (Pongbunroad, 1965;

Bunyapraphatsara, 1986). The powder of turmeric dissolved in water is applied on the skin to kill some bacteria and fungi, to heal wounds and reduce itching in skin diseases (Pongbunroad, 1965; Bunyapraphatsara, 1986; Farnsworth and Bunyapraphatsara, 1992; Imwittaya, 1983; Shankar and Murthy, 1979). It is cooked with coconut oil, and used as an astringent for wounds (Tontiwat, 1978; Pongbunroad, 1965; Bunyapraphatsara, 1986). In addition turmeric has long been customarily used in cosmetics for ladies by applying the mixture of turmeric and honey preparation over the body skin. Water extract or powder of turmeric mixed with human breast milk can treat allergic conjunctivitis in baby (Assawapantanakul, 1990).

Turmeric is a herb that the Ministry of Public Health declares as a fundamental drug for the primary health care. The usage of this plant appeared in the public health policy of the Thai government as inscribed in the 5th National Economic Development Plan (1982 - 1986) (Vuthipongse, 1986; Sithicharoenchai, 1986). Turmeric is one of five medicinal plants used efficiently as single drug *ie* not combined with other plants in the formulation (Vuthipongse,1986; Sithicharoenchai, 1986; Suppasil - Nanakorn, 1993). These five plants are turmeric, aloe /star cactus, Fathalaichon (in Thai), Phayayoh (in Thai) and ringworm bush. The Ministry of Public Health promotes the single usage of these medicinal plants. The development of holistic knowledge for the purpose of producing these five medicinal herbs as prescription drugs, was announced in the 6th National Economic Development Plan (1987 - 1991) (Suppasil - Nanakorn, 1993).

Turmeric is known as a condiment and spice exported product, amounting to approximately 39.8 tons per year and is used by the traditional medicine industry (approximately 6.036 tons per year) (Bunyapraphatsara *et al*, 1981).

From traditional medicine, doctors used turmeric orally for regulation of health (Pongbunroad, 1965; Farnsworth and Bunyapraphatsara, 1992). According to the ancient belief, the human body consists of four elements namely, earth, water, air and fire. The digestion is a fire element. Turmeric may promote health by regulating at least the fire element (Sethaputra, 1980; Bunyapraphatsara, 1992).

The purpose of this study was to assess the efficiency and safety of turmeric, and its action when used in large numbers of patients in a period of four weeks. The studied measurements were endoscopical change in epithelial mucosa corresponding with patients' symptoms. Turmeric was delivered in capsules instead of the traditional pills. Efficacy and safety were assessed. This study also benefits the conservation of Thai traditional medicine.

MATERIALS AND METHODS

Ethics

The study was approved by the Ethics Review Committee of the Faculty of Medicine Siriraj Hospital, Mahidol University. All subjects gave written informed consent to participate.

Study population

The patients with abdominal pain which indicated peptic ulcer as well as patients in a state of acute exacerbation were selected in this study during 1987-2001. Their ages ranged from 16-60 years and both sexes were included. The criteria for exclusion of patients from the study were heart disease, hepatic, renal, hypertension, cancer, pregnancy, and brain arteriosclerosis. Endoscopy was performed to determine the pathology of mucous epithelial lining. Only patients who had 0.5-2 cm in diameter of the ulcer were selected and taken pictures of some in this study. Each patient was treated with 300 mg turmeric capsules, 2 capsules each time and 5 times per day by taking 30-60 minutes before meals, at 4 pm and before bedtime until there was no pain and ulcers. The patients were endoscoped again after 4, 8 and 12 weeks of turmeric treatment. The results before and after treatment were analyzed statistically with the Student's *t*-test method (the paired data analysis). The report showed the percentage of healing in every 4 weeks.

Study design

This was an open study. Each patient realized receiving turmeric. It was a pilot study (clinical trial phase II).

Herbal medicine

The turmeric capsules, as a herbal medicine, were prepared from crude powder of dried rhizome of *Curcuma longa* Linn. The crude turmeric powder was filled in capsule number one to make each capsule 300 mg dosage. The initial idea of using capsules, the modern pharmaceutical dosage form, instead of pills which had been used customarily in Thai traditional medicine, came from Siriraj Hospital (Prucksunand *et al*, 1986; Division of Medicinal Plant Research and Development, 1990; Prucksunand, 2001).

The method of preparing turmeric pills-powder (Assawapantanakul,1981) was imitated for modern pharmacy of capsules-powder development (Division of Research and Development, 1990).

Safety

To study the side effects of turmeric, blood chemistry and hematology were performed. Blood samples were taken from the cubital vein before and after treatment. The blood chemistry and hematology were performed in all 45 patients, some of whom had history of peptic pain even though no ulcer was found by endoscopy. They had gastritis, duodenitis or erosions. Those patients who refused to have endoscopy examination were studied for blood chemistry and hematology to assess the safety of this medicinal plants.

RESULTS

Twenty-five patients had symptoms of abdominal hunger pain, epigastric pain, vomiting, hematemesis and melena. They were studied by endoscopy to assess ulcers in the stomach and duodenum. Their ulcer sizes were between 2 x 6 to 15 x 15 mm^2 (Table 1). After the capsule-filled turmeric was given orally in the dose of 2 capsules (300 mg each) five times daily, the endoscopic examinations were done periodically at 4, 8 and 12 weeks. The percentages of ulcer healing were 48% (12 cases), 72% (18 cases) and 76% (19 cases) after 4, 8 and 12 weeks of treatment respectively. No serious adverse effects were found in all patients (Tables 2, 3).

The conventional statistical methods used was Student's *t*-test for paired analysis. Comparing the control group, before treated and the after treated group in the same patients showed significant differences ($p < 0.05$).

DISCUSSION

The effect of turmeric on healing of peptic ulcer was studied by endoscopy in 25 patients (17 men, 8 women). There were 20 cases with duodenal ulcer and 5 cases with gastric ulcer. Nineteen of 25 patients (76%) had no more ulcers after turmeric treatment for 4-12 weeks. For the detail of healing, in 4 weeks the heal rate was 48% (12 of 25 patients). After 8 weeks of treatment, the rate of ulcer absence was increased in 6 of 25 patients (24%). In 12 weeks, the healing rate was 8% (2 from 25 patients). It was apparent that for the patient # 18, the first ulcer disappeared within 8 weeks, and the new ulcer which found on the fourth week of the study also healed in 8 weeks, but the total time of turmeric treatment course in this case was 12 weeks. Patient # 4 was a heavy smoker, so it took longer time for healing *ie*, 12 weeks. Turmeric had no effect in patients # 12, 14, 15, 19 and 20 (20% failure rate).

The ulcer size did not decrease in patients # 19 and 20 after treatment for 4 weeks and their ulcers were as large as 10 mm. The patients were then given turmeric combined with ulsanic. In case # 12, the size of new duodenal ulcer found on 8 weeks was increased from 3x3 to 5x5 mm^2 at 12 weeks. Therefore the drug was changed. The abdominal pain was more severe in patients # 14 and 15 after eating turmeric, therefore the study was stopped and the medicine was changed. Patients # 16 and 17 (males, 63 and 53 years of age) had

Table 1
The effect of turmeric capsule (*Curcuma longa* Linn) on healing of peptic ulcer (Case Nos. 1-25).

Case no.	Age (years)	Sex	Symptom	History (causes)	Ulcer		Frequency (cases)	Duration of treatment		
					Size (mm^2)	Location		4 weeks	8 weeks	12 weeks
								Ulcer		
1, 2	68, 58	M	abdominal pain 2 days melena 7 days	take indocid for knee joint, take analgesic	2 x 6 2 x 8	DU (anterior) DU (anterior)	2	absent (3 wks)		
3	29	M	hungry abdominal pain	not on time for eating, study hard, serious stress	3 x 4	GU (posterior)	1	absent (no pain since 2 wks)		
4	56	F	abdominal pain 10 yrs, epigastric pain	heavy smoke, analgesic, not on time for eating, eating spicy food 10 yrs	3 x 8	DU (superior)	1	(3 x 7)	(3 x 5)	absent (white scar)
5	31	M	hematemesis one day	take analgesic for headache	5 x 5	GU (angulus)	1	absent		
6,7,8	50,40,30	F	vomiting 2 days, melena 4 wks	not on time for eating	5 x 5	DU (anterior)	3	absent		
9,10,11	28,38,48	M	hematemesis 7 days, the blood stop at hospital	not on time for eating, smoke, analgesic,	5 x 5	DU (base)	3	red scar	absent	
12	29	M	hematemesis 4 days, melena 4 days	not on time for eating, alcohol, smoke, analgesic,	5 x 5	DU (anterior)	1	red scar	new DU (inferior) (3x3)	DU (inferior) (5x5), change the medicine
13	16	M	melena 1 wk	study hard, tired work, serious life style	7 x 7	DU (inferior)	1	absent		
14, 15	34, 44	M	epigastric pain, eructation 1 wk	alcohol drink, heavy smoke, analgesic	7 x 7	DU (anterior)	2	same size, fail change medicine		
16	63	M	melena one day	analgesic for knee pain	7 x 7	DU (superior)	1	absent		
17	53	M	melena one day	analgesic for knee pain	8 x 8 7 x 7	GUI GU II	1	absent		
18	48	M	hematemesis one day, melena one day	not on time for eating, working hard, late sleep	10 x 10	DU (inferior) H_1stage	1	(5 x 5), new DU (inferior) (5 x 10)	absent H_1stage (5 x 10)	absent
19, 20	20, 30	M	midnight abdominal pain, melena 2 wks	smoke, analgesic, not on time for eating 1 yr	10 x 10	DU (bulb)	2	same size, fail change medicine		
21, 22	39, 29	F	gas abdominal pain, epigastric pain	not on time for eating, smoke, analgesic, coffee 4-5 yrs	10 x 10	GU (angulus) (prepyloric)	2	(5 x 10)	absent (6 wks)	
23	47	M	abdominal pain 7 days	heavy smoke, drink	13 x 13	DU (superior)	1	(10 x 5)	(5 x 5) (no abdominal pain)	loss follow-up
24, 25	21, 31	F	empty abdominal pain 3 days	not on time for eating, worry character	15 x 15	DU (bulb)	2	absent		

Table 2
Average values of blood chemistry of 45 patients before and after 4 weeks period of turmeric treatment.

Blood chemistry	Normal values	Before treatment	4 weeks after treatment
Blood sugar	70 - 110 mg/100 ml	95.9	99.5
BUN	10 - 20 mg/100 ml	10.6	12.9
Creatinine	0.7 - 1.4 mg/100 ml	1.1	1.2
Uric acid	2.5 - 8.0 mg/100 ml	5.0	5.8
Total protein	6 - 8 g/100 ml	6.7	7.1
Albumin	3.5 - 5.0 g/100 ml	3.9	4.0
Globulin	2.5 - 3.0 g/100 ml	2.8	2.9
Total bilirubin	0.15 - 1.0 mg/100 ml	0.8	0.8
SGOT	8 - 40 mU/ml	18.1	19.9
SGPT	8 - 40 mU/ml	14.6	19.0
Cholesterol	150 - 300 mg/100 ml	164.1	162.9
Triglycerides	55 - 170 mg/100 ml	143.7	96.5
Alkaline phosphatase	30 - 85 mU/ml	40.4	37.4
Sodium	135 - 145 mmol/l	139.6	142.1
Potassium	3.5 - 5.0 mmol/l	4.3	4.3
Calcium	8.5 - 10.5 mg/100 ml	9.5	9.2
Chloride	95 - 105 mg/100 ml	100.0	98.0
Phosphorus	2.5 - 4.5 mg/100 ml	3.9	3.8
Bicarbonate	24 - 32 mmol/l	26.3	26.2

Table 3
Average values of hematology of 45 patients before and after 4 weeks period of turmeric treatment.

Hematology	Normal values	Before treatment	4 weeks after treatment
RBC	4.0 - 6.0 x 10^{12} /mm^3	4.42	4.47
Hemoglobin	13 - 17 g/100 ml	13.34	13.33
Hematocrit	37.3 - 42.7 %	39.1	40.0
Platelets	150,000 - 400,000 per mm^3	adequate	adequate
WBC	5,000 - 10,000 per mm^3	7,054	7,421
Differential			
Neutrophils	40 - 75 %	62.6	57.1
Band	0 %	0.5	0.9
Eosinophils	1 - 6 %	3.9	3.6
Basophils	0 - 1 %	0.1	0.3
Lymphocytes	20 - 60 %	29.5	34.9
Monocytes	2 - 10 %	3.4	3.2

knee pain history and took analgesics daily. These patients had hypertension, diabetes mellitus and a previous history of admission to hospital with melena and hematemesis. They received cimetidine but were satisfied with turmeric. They preferred medicinal plant and traditional medicine more than modern medicine. These patients received turmeric on this project at the time when they had no hematemesis. These patients were admitted to the hospital several

times because of stomach bleeding. Patient # 23 had subsided from abdominal pain since 8 weeks, but was lost on follow-up.

A multicenter trial (Vantrappen, 1980) found that small ulcer (less than 5 mm) can be healed by nature or treatment with placebo 38.9% in four weeks. From our study, turmeric could heal approximately 76% of ulcers in 4-12 weeks. The detail was as follows ; 48% healed in 4 weeks, 72% healed in 8 weeks and 76% healed in 12 weeks which indicated that turmeric had fair healing property for peptic ulcer. This study showed the corresponding result with Vantrappen's report of treatment with prostaglandin (15-R-15-methyl prostaglandin E_2) for 62.8% in 4 weeks (Vantrappen, 1980). The lower effect of turmeric may be due to using crude drug. If the active compounds were purified, turmeric may give better results but the cost is expensive.

The physician should explain and pay attention to the patients in order to get the best result. The patients will be calm, have no stress and receive the remedy with confidence. The patient-doctor relationship in traditional medicine is important. In addition to turmeric, honey was also given 1-2 table-spoonful each time with turmeric to some patients *ie*, cases # 9, 10, 11, 13, and 18 for imitating the traditional medicine which mixed and made pills of turmeric with honey. The other patients did not have honey. In our study the preparation of turmeric capsule was made without honey for convenience and not easily spoiled.

It is apparent that Thai empirical medicine experienced the promotion of ulcer healing by giving honey (Assawapantanakul, 1981 ; 1990). A study of chronic wound healing by dressing with honey was done in Thailand (Dumronglert, 1987). The selection of giving honey was done in patients who ate turmeric alone and in the first 1-2 weeks their abdominal pain did not reduced. Honey reduced hypoglycemia and the patient got normal blood sugar from honey. Hypoglycemia stimulated the gastric acid secretion and contraction of smooth muscle of gastro-intestinal tract by hypothalamico-pituitary-adrenal concept (Sun, 1974). Honey decreased stimulation of acid secretion via glucose. However, the patient who did not receive honey showed the healing effect similar to patient with honey. This indicated that turmeric alone had property to cure ulcer.

The chemical structures of *Curcuma longa* Linn. studied by Stransky (1979), Srinivasan (1953) and Rupe *et al* (1934) were found to be curcumin, curcuminoids and turmerone respectively. The active ingredients acted as anti-peptic ulcer was proposed to be curcumin or turmerone.

The proposed mechanism of action in healing ulcer of turmeric is numerous. Previous reports stated that turmeric was a local anesthetics (Supniewski and Hano, 1935) and relieves itching (Farnsworth and Bunyapraphatsara, 1992).

The effect of turmeric on frog nerve action potential showed the property of a blocking agent (Prucksunand, 2000). Farnsworth and Bunyapraphatsara (1992), Supniewski (1935) and Prucksunand (2000) explained that turmeric had local anesthetic action. After eating turmeric, gastrin hormone secretion from the antrum of the stomach may be inhibited. Turmeric may possess local membrane anesthetizing activity at antrum of stomach then inhibits gastrin in the same way as oxethazaine, which is the active ingredient of strocain (Masuda, 1973). This is the reason to administer turmeric before meals. Gujral *et al* (1953) found that turmeric had the property of healing of wounds and ulcers in rats and rabbits. The finding that stimulation of mucin secretion could protect the stomach from ulcer was shown in rabbits (Mukerji *et al*, 1961). Curcumin is the ingredient that stimulates mucin secretion (Sinha *et al*, 1975). A protective effect of turmeric against HCl-induced gastric necrosis was shown in rat (Prucksunand, 1997). A high dose of curcumin 100 mg/ kg can induce gastric ulcer in rats (Gupta *et al*, 1980). Curcumin and its derivatives possess antioxidant activity (Sharma, 1976; Oyama *et al*, 1998). Curcumin could offer a defense mechanism and may lead to protection of erythrocyte cellular membrane from damage (Salimath, 1986). Curcuminoid

from *Curcuma longa* Linn. protected human keratinocytes from oxygen radical injury (Bonte *et al*, 1997). This preventive mechanism of turmeric on peptic ulcer needs further proof.

Another interesting property of turmeric is antibacterial activity, especially on enteric bacteria (Farnsworth and Bunyapraphatsara, 1992). The antioxidant curcumin showed inhibition effect on NF-kappa B activation and also IL-8 induction by *Helicobacter pylori* (Munzenmaier *et al*, 1997). This will explain the anti *H. pylori* effect of turmeric and then the treatment of peptic ulcer. Few patients in our study were determined for *H. pylori*, only one patient had positive result. In future, it is a challenge to study turmeric on peptic ulcer and *H. pylori* infection.

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