

# A Randomized Clinical Trial of Curcumin in the Maintenance Therapy of Ulcerative Colitis

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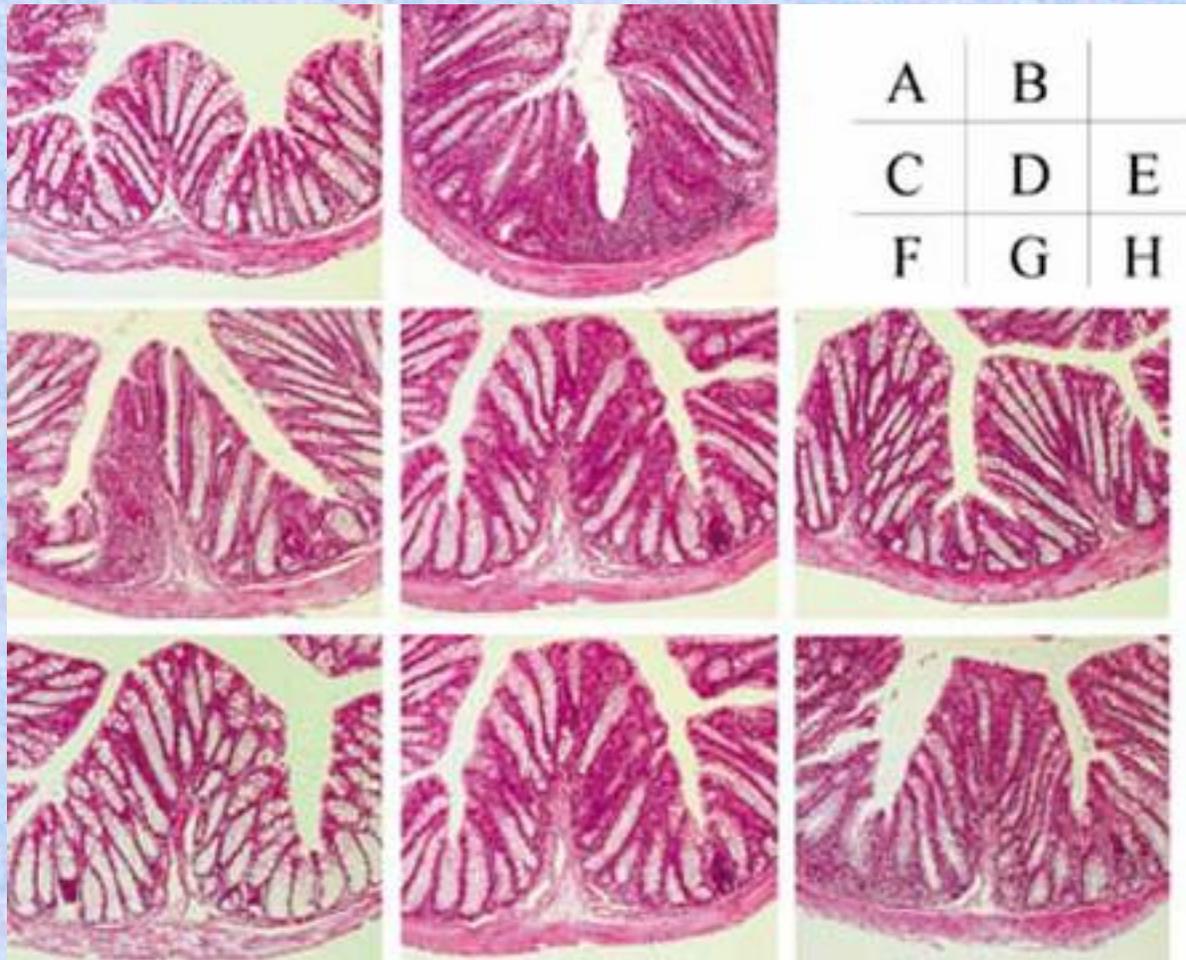
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# ***Background***

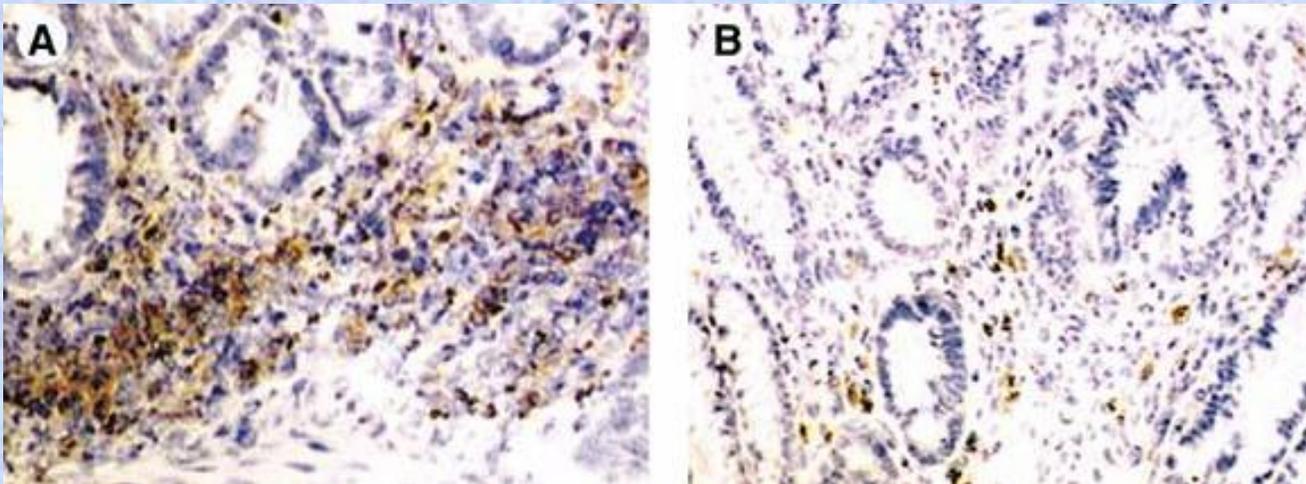
**Drugs, such as corticosteroids, used for treatment of patients with inflammatory bowel disease (IBD) cause many side effects. Therefore, medications that cause minimal side effects are desired for the treatment. Curcumin, widely used as a spice and responsible for the yellow color of curry, is a natural product of plants. We have demonstrated that treatment with curcumin is able to prevent and improve murine experimental colitis (TNBS-induced colitis) by suppressing NF- $\kappa$ B activation (Fig. 1, 2) and CD4+ T cell infiltration (Fig. 3) and proinflammatory cytokine mRNA expression (Fig. 4) in colonic mucosa. These results suggest that curcumin may be of therapeutic value for patients with IBD.**

# Fig.1. Histological analysis of the colon in C57BL/6 mice



**(A) Normal architecture of the colon mucosa. (B) Administration of TNBS elicits distortion of crypts, loss of goblet cells, and infiltration of mononuclear cells. (C-E) TNBS-induced colitis is dose-dependently improved by curcumin. Mice were fed with (C) 0.5%, (D) 2.0%, or (E) 5.0% curcumin just after administration of TNBS. (F-H) Improvement of TNBS-induced colitis is affected by timing of curcumin administration. Mice were fed with 2% curcumin in (F) preventive mode, (G) day 0 or (H) day 2 after TNBS administration.**

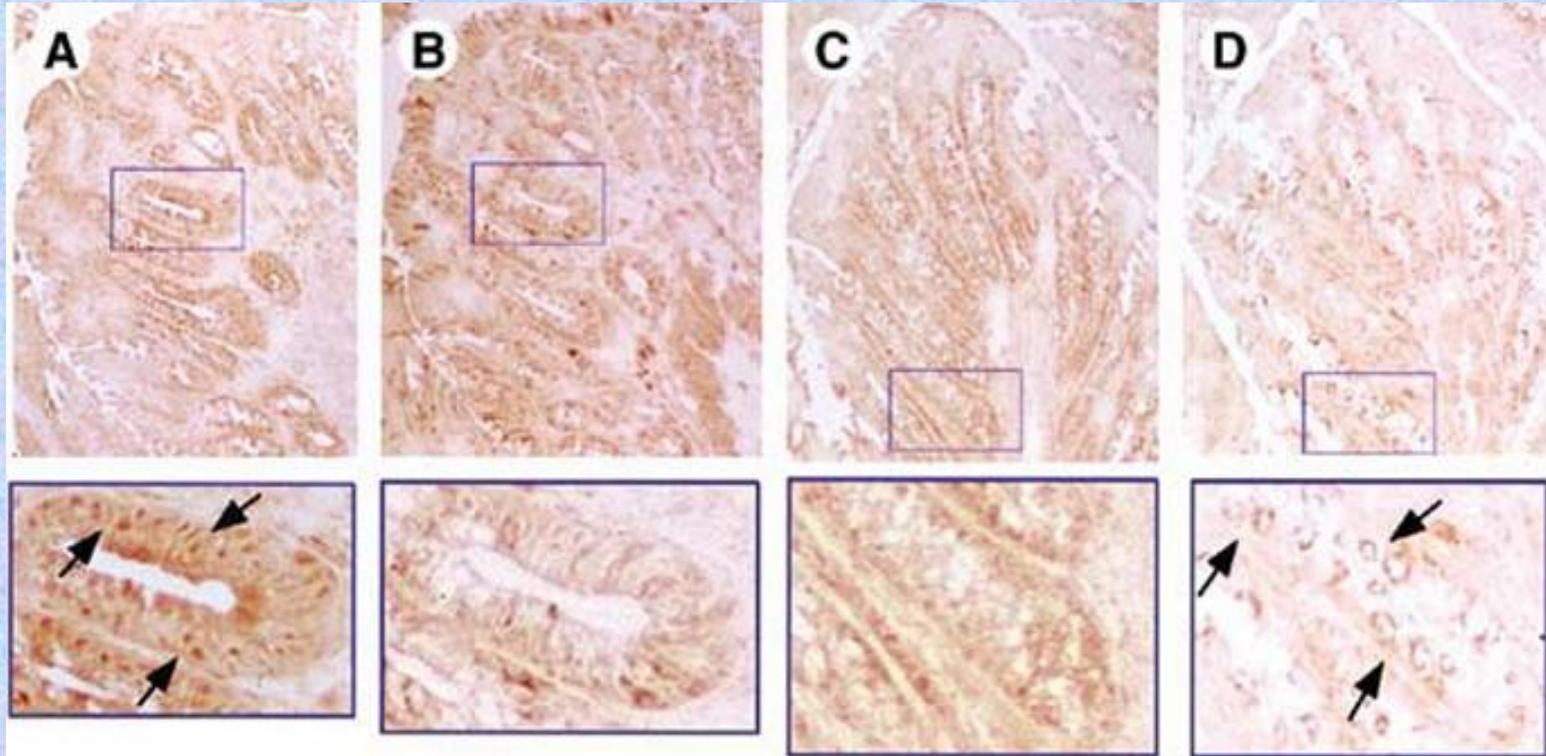
## **Fig.2. Detection of CD4+ T cells in colonic mucosa.**



**(A) TNBS-induced colitis.**

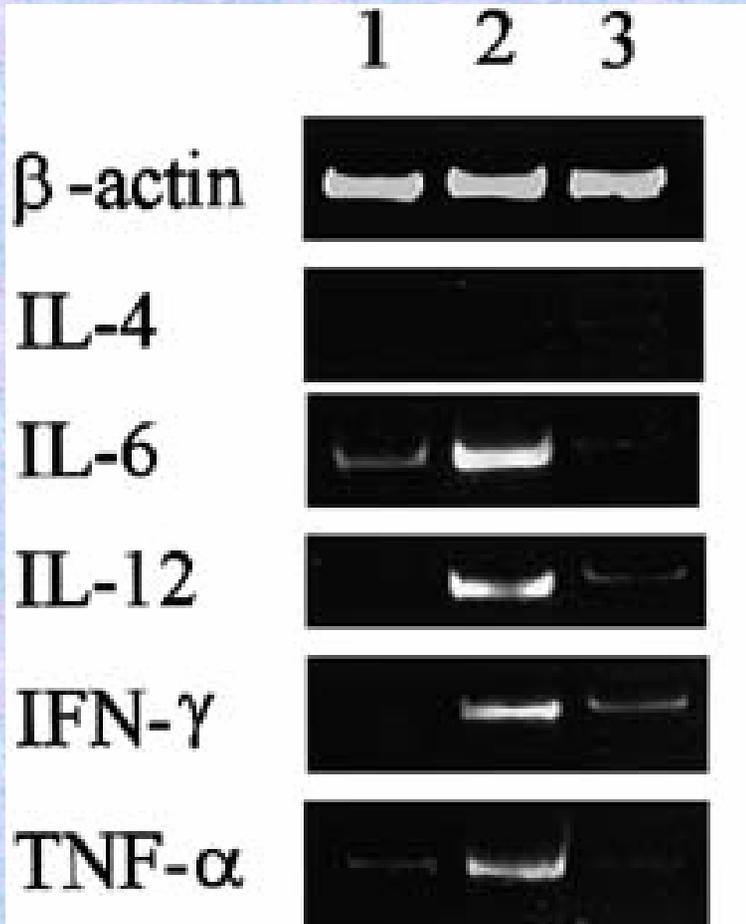
**(B) 2.0% curcumin-treated mice with TNBS-induced colitis.**

### Fig.3. Effect of curcumin treatment on NF- $\kappa$ B activation *in situ*



Tissue sections from (A and B) untreated mice with TNBS-induced colitis and (C and D) 2.0% curcumin-treated mice with TNBS-induced colitis. Specimens were stained immunohistologically with (A and C) anti-p65 and (B and D) I B Abs. In untreated mice with TNBS-induced colitis, p65 was detected in epithelial nuclei (A; arrows) but not in 2.0% curcumin-treated mice. (C) Staining for p65 in nuclei was unclear. In contrast, I B was stained for around epithelial nuclei in a ring-shaped configuration in 2.0% (D; arrows) curcumin-treated mice but not stained for in (B) untreated mice with TNBS-induced colitis.

**Fig.4. Detection of mRNAs in colonic mucosa for cytokines by RT-PCR**



1. Control
2. TNBS
3. 2.0% curcumin just after administration of TNBS

# ***Clinical trial***

The **aim** of this clinical trial is to investigate the efficacy of curcumin in maintaining remission stage in ulcerative colitis (UC) in a randomized placebo-controlled double-blind fashion.

**Treatment protocol** is as follows;

## **Group 1:**

50 patients will be treated with 4 g of curcumin only with SASP/5-ASA.

## **Group 2:**

50 patients will be treated with 4 g of placebo only with SASP/5-ASA. The patients who receive corticosteroid or immunosuppressant (6 MP/ Azathiopurin) are excluded. Groups 1 and 2 will be performed in a randomized fashion.

# Scheme of clinical trial

	<i>Observation Period</i>	<i>Start</i>	<i>4 weeks</i>	<i>12 weeks</i>	<i>24 weeks</i>	<i>48 weeks</i>
<i>Written informed consent</i>	✓					
<i>Inclusion/exclusion criteria</i>	✓					
<i>Drug administration (Twice/day)</i>						
<i>Efficacy assessment</i> ✓ <i>Symptoms recorded in the diary</i> ✓ <i>CAI score*</i> ✓ <i>Colonoscopy (including biopsy)</i>						
	✓ ✓	✓	✓	✓	✓ ✓	✓ ✓
<i>Safety assessment</i> ✓ <i>Unfavorable and unexpected symptoms</i> ✓ <i>Laboratory studies</i>						
		✓	✓	✓	✓	✓

# Examination

- ✓ Endoscopy combined with histological examination in biopsy specimens.
- ✓ The histological studies, pathological grading measurements by immuno-histochemical study and cytokine mRNA by real time RT-PCR.
- ✓ Clinical activity index (CAI) according to Rachmilewitz's criteria (CAI, EI).
- ✓ Patients who show  $CAI \leq 4$  are regarded as in remission stage (success).
- ✓ We consider  $CAI > 5$  or three-fold gain in CAI as compared with previous value to be failure of the treatment and the patients will be terminated from the study.

# Present Situation

**Total number of patients: 82**

**Randomization**

**Curcumin (4 gr/day)**  
**41 cases**

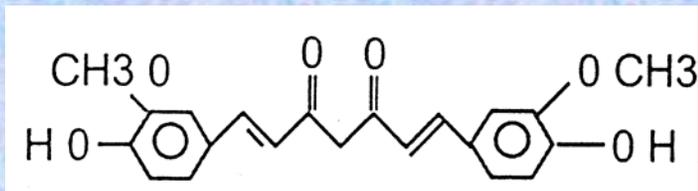
**Placebo(4 gr/day)**  
**41 cases**

Withdrew due to flare up: 4 cases  
Patient withdrew at will: 2 cases  
Ineligible: 1 case

*(patient was taking an immunosuppressant)*

## Curcumin

Components	%
Curcumin	50.0
Microcrystalline Cellulose	42.5
Maltitol	7.5
<b>Total</b>	<b>100.0</b>



Curcumin (Diferuloylmethane)

## Placebo

Components	%
Microcrystalline Cellulose	25.000
Dextri	29.593
Corn starch	10.000
Maltitol	35.000
FD & C Yellow No.5	0.150
FD & C Yellow No.6	0.037
Caramel Color	0.220
<b>Total</b>	<b>100.000</b>

# Clinical Activity Index (CAI; Rachmilewitz)

1) No of stools weekly	<18 18 — 35 36 — 60 >60	0 1 2 3
2) Blood in stool	None Little A lot	0 2 4
3) Investigator's global assessment	Good Average Poor Very poor	0 1 2 3
4) Abdominal pain/cramps	None Mild Moderate Severe	0 1 2 3
5) Temperature due to colitis	37 — 38 >38	0 3
6) Extra intestinal manifestations	Iritis Erythema Nodosum Arthritis	3 3 3
7) Laboratory findings	ESR >50 min in 1h ESR >100 min in 1h Haemoglobin <10g/l	1 2 4

# Patients

Demography	Measurements
Male/female	44/38
Age, mean; range (yr)	39.7; 15-68
Duration of UC (month)	64.6
Time remission sustained (month)	9.9; 2- 24
Number of recurrences in the past two years	1.7; 0-5
Clinical course:	
• First attack	9 cases
• Relapsing-remitting	53 cases
• Chronic continuous	20 cases
Extent of UC:	
• Total colitis	33 cases
• Left sided colitis	49 cases

# Safety

**A total of 7 non-severe and transient side effects in 7 of 82 patients were observed during curcumin maintenance therapy.**

**These were:**

- 2 sensation of abdominal bulging,**
- 2 incidences of nausea,**
- 2 constipation**
- 1 hypertension (discontinued)**
- 1 transient increase in the number of stools**
- 1 elevated  $\gamma$ GTP level (43  $\rightarrow$  78 IU/L)**

**However, no patient discontinued the therapy due to these side effects, except the patient with hypertension.**

# ***The hospitals and doctors involved in this study***

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**Drs. Hajime Arai and Shigehito Yoshii**
9. Sendai Shakai Hoken Hospital  
**Dr. Mitsunori Noguchi**