RESEARCH ARTICLE

Effects of Curcumin on the intestinal length and morphology: An experimental study in albino rats

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Received: 13.06.2011

Accepted: 08.08.2011

ABSTRACT

Aims: This study was carried out to evaluate the effect of curcumin on small intestinal length and morphology.

Materials and methods: Rats were divided into 5 groups (Group I - Group V), based on the time interval between administration of curcumin/vehicular fluid to the sacrifice of the rats (Group I – 1 hr, Group II – 8 hr, Group III – 16 hr, Group IV – 24 hr, Group V – 48 hr). Each group was further divided into two sub-groups, Group A (control) and Group B (experimental). Rats in Group A were given vehicular fluid (0.9% NaCl) while the rats in Group B were administered curcumin intragastrically by the naso-gastric tube reaching up to the lower 1/3rd of oesophagus, in the dose of 1 gm/kg body weight, suspended in normal saline.

Results: After the intra-gastric administration of single dose of curcumin, there was an increase in the small intestinal length in all the experimental groups as compared to control groups. Morphometric analysis showed that the numbers of mitotic figures were less in case of experimental group as compared to control groups. However no statistically significant differences in microscopic structure of duodenum, jejunum and ileum were observed between control and experimental groups.

Conclusion: These data suggests that curcumin reduces resting tone of intestine and this may be the reason for increase in length of intestine in albino rats. This may partly explain the traditional use of curcumin as antispasmodic agent.

KEY WORDS: Curcumin; resting tone; intestine length; morphology

INTRODUCTION

Worldwide interest in natural products as preventive and therapeutic agents has led to a greater appreciation of the rich heritage of traditional system of medicine. Turmeric (Curcuma longa L) is a medicinal plant extensively used in Ayurveda, Unani and Siddha medicine as home remedy for various diseases. Curcuma longa L, botanically related to ginger family, is perennial plant having a short stem with pyriform rhizomes. Curcumin, the main yellow bioactive component of turmeric has been shown to have a wide spectrum of biological actions. Curcumin has been used for the treatment of cough, fever, liver diseases, wound healing, inflammatory conditions of joints.[1-8] Recent studies, in the human beings and the experimental animals have shown the beneficial effect of curcumin on the function of the gastrointestinal tract. It increases bile secretion in the anesthetized dogs and rats.[9] It elevates the activity of pancreatic lipase, amylase, trypsin and chymotrypsin.[10] Sodium curcuminate inhibit castor oil induced diarrhoea suggesting action of drug on the smooth muscle cells of gastrointestinal tract.[11] Turmeric is the main ingredient of many food additives used at home all over the country. The mucosal surface of the gastrointestinal tract is periodically but regularly exposed to turmeric. Because of continued exposure of mucosa of gastrointestinal tract to turmeric, there is a distinct probability that it may cause changes in the structure and functions of gastrointestinal tract. However studies on the effect of curcumin on the structure of gastrointestinal tract are nearly nonexistent. For this reason the present study was undertaken.

MATERIALS AND METHODS

Animals

Albino rats of wistar strain, weighing 130-170 gm, of either sex, raised under standard laboratory conditions were obtained from Indian Veterinary research institute, Izat Nagar, Barellie, Uttar Pradesh. The animals were housed in polycarbonate cages of size 35cm x 23cm x16cm. 4 rats per cage were kept. The animals were fed cooked food ad labium with free access to water. All experiments on rats were carried out in accordance with the recommendation of CPCSEA guidelines for care and use of laboratory animals and the study was approved by Institutional Animal Ethics Committee.

Drugs

Curcumin

Curcumin was obtained in the form of capsule containing 500mg of Curcumin from INDSAFF, Batala. Curcumin (diferuloylmethane), a polyphenol, is an active principle of the perennial herb Curcuma longa. The yellow-pigmented fraction of turmeric contains curcuminoids, which are chemically related to its principal ingredient, curcumin. The major curcuminoids present in turmeric are demethoxycurcumin (curcumin II), bisdemethoxy-curcumin (curcumin III), and the recently identified cyclocurcumin. The major components of Commercial curcumin are curcumin I (77%), curcumin II (17%), and curcumin III (3%).

Dosage

Dose of curcumin was calculated as per 1 gm/kg body weight.[12] Curcumin from the capsule was dissolve into 5 ml normal saline (0.9% NaCl) to make suspension of the drug.

Meter Scale

A metal meter scale fitted on hard board was used to measure the length of intestine and distance travelled by the barium.

Acute Toxicity Study

6 rats were taken for acute toxic effect of curcumin. The animals were fasted overnight and the curcumin was administered intragastric in the dose of 2 gm/kg boby weight. Animals were observed continuously for first 3 hrs. and were monitored for three days for mortality and general behaviour of animals, signs of discomfort and nervous manifestations. No mortality and adverse effects were observed with this dose.

Experimental Protocol

60 rats were divided into 5 groups (Group I - Group V), based on the time interval between administration of curcumin/vehicular fluid to the

sacrifice of the rats (Group I – 1 hr, Group II – 8 hr, Group III – 16 hr, Group IV – 24 hr, Group V – 48 hr). Each group was further divided into two sub-groups, Group A (control) and Group B (experimental), containing 6 rats each. Rats in Group B were administered curcumin intragastrically by the naso-gastric tube reaching up to the lower 1/3rd of oesophagus, in the dose of 1 gm/kg body weight, suspended in normal saline while rats in Group A were given vehicular fluid (0.9% NaCl) in equal volume as that of curcumin suspension given to experimental group.

After requisite time as per Group I – Group V, in both the groups, (experimental & control) rats were sacrificed by cervical dislocation. Abdomen was opened by midline incision and ligatures were applied at the gastroduodenal junction and ileocaecal junction. The small intestine was stripped of the mesentery and taken out of the abdomen and laid over a board fitted with a meter scale. The upper surface of board was kept continuously wet with normal saline. The length of the intestine was measured by placing it closely along the meter scale.

Morphological Studies

For morphological evaluation, tissue specimens were sent from each group. The intestine was washed with normal saline, soon after the small intestine was filled with 5% formal saline after securing it between two ligatures (at gastro duodenal junction and ileocaecal junction) and transferring to the same fluid for fixation. After dehydration the tissue was embedded in paraffin. Sections were cut at 3-4 µm and stained with hematoxylin and eosin. The sections were examined under microscope at 10X, 40X, 100X. For morphometery, an ocular micrometer was used at a magnification of 40X.

Analysis of Data

Mean and standard error of all the observations were calculated and comparisons were done between experimental and control groups by applying Student "t" test (unpaired). Comparisons of the effect of curcumin on the intestinal length amongst different experimental groups were done applying one way ANOVA.

RESULTS

After the intra-gastric administration of single dose of curcumin, there was increase in small intestinal length in all the experimental groups as compared to control groups. In Group I to Group III, the increase was statistically significant, while in Group IV and Group V it was statistically insignificant. The increase in intestinal length was maximum at 16th hr of curcumin administration (table-1).

Table-1: Comparisons of effect of curcumin on the length of small intestine (Mean ± SEM) following intra-gastric administration of single dose of curcumin (1 gm/kg body wt) in control and experimental groups

Groups	Length of small intestine (cm) (Mean ± SEM)		P value
	Control (A)	Experimental (B)	
Group I	102.5 ± 1.335	110.5 ± 1.839	<0.01**
Group II	102.7 ± 1.282	113.8 ± 1.721	<0.01**
Group III	104.8 ± 1.138	115.7 ± 1.116	<0.001***
Group IV	103.5 ± 1.335	106.8 ± 1.108	>0.05
Group V	103.3 ± 0.9189	105.5 ± 0.6708	>0.05

*P-value < 0.05: significant, **P-value < 0.01: highly significant, ***P-value < 0.001: very highly significant, P-value >0.05: insignificant

On applying one way ANOVA in different groups of experimental animals F value was 10.28 and P value was less than 0.0001 which was statistically highly significant (table-2).

Table-2: Comparisons of effect of curcumin on the length of small intestine following intra-gastric administration of single dose of curcumin (1 gm/kg body wt) in different experimental groups by one way analysis of variance

	Sum of squares	Df	Mean square	F	P value
Regression (between column)	457.5	4	114.4	10.28	<0.0001
Residual (with in column)	278	25	11.12		
Total	735.5	29			

*P-value < 0.05: significant, **P-value < 0.01: highly significant, ***P-value < 0.001: very highly significant, P-value >0.05: insignificant

Table-3: Comparison of mean value of histological observations of duodenum in control and experimental groups (values expressed as Mean ± SEM)

Sr. No.	Duodenum						
	Parameters	Control	Experimental Groups				
			Group I	Group II	Group III	Group IV	Group V
1	Shape of villi	Leaf/finger shaped	Leaf/finger shaped	Leaf/finger shaped	Leaf/finger shaped	Leaf/finger shaped	Leaf/finger shaped
2	Position of villi	Upright	Upright	Upright	upright	Upright	Upright
3	Height of villi	69.2 ± 8.3	70.6 ± 5.4	70.2± 5.8	68.9 ± 6.2	69.4 ± 7.4	67 ± 5.2
4	Inflammatory	Absent	Absent	Absent	Absent	Absent	Absent
5	Hemorrhage	Absent	Absent	Absent	absent	Absent	Absent
6	No. of goblet cell/crypt/HPF	8.2 ± 1.4	8.4 ± 0.8	8.5 ± 1.2	8.2 ± 0.9	8.2 ± 1.3	8.3 ± 1.6
7	No. of columnar cells/crypt/HPF	39.1 ± 1.8	38.8 ± 1.7	36.6 ± 2.1	41.1 ± 2.4	38.7 ± 1.9	40.2 ±.8
8	No. of Mitotic cells/crypt/HPF	5.5 ± 1.1	5.1 ± 1.5	4.6 *± 1.1	4.9 ± 1.7	5.3 ± 1.1	5.1 ± 1.6

Table-4: Comparison of mean value of histological observations of jejunum in control and experimental groups (values expressed as Mean ± SEM)

Sr. No.	Jejunum						
	Parameters	Control	Experimental Groups				
			Group I	Group II	Group III	Group IV	Group V
1	Shape of villi	Leaf/finger shaped	Leaf/finger shaped	Leaf/finger shaped	Leaf/finger shaped	Leaf/finger shaped	Leaf/finger shaped
2	Position of villi	Upright	Upright	Upright	Upright	Upright	Upright
3	Height of villi	107 ± 8.3	110.6 ± 9.4	109.2± 8.8	108.9±10.5	110.2±11.4	106 ±9.2
4	Inflammatory	Absent	Absent	Absent	Absent	Absent	Absent
5	Hemorrhage	Absent	Absent	Absent	Absent	Absent	Absent
6	No. of goblet cell/crypt/HPF	7.8 ± 1.4	8.2 ± 1.8	7.6 ± 1.2	7.82 ±1.9	8.1 ± 1.1	7.8 ± 1.6
7	No. of columnar cells/crypt/HPF	39.5 ± 1.1	38.8 ± 1.6	39.6 ± 1.9	40.1 ± 2.4	38.7 ± 1.7	39.2 ±1.8
8	No. of mitotic figure/crypt/HPF	4.5 ± 0.6	4.2 ± 0.8	4.1 ± 0.7	4.3 ± 0.7	4.2 ± 0.5	4.3 ± 0.6

Table-5: Comparison of mean value of histological observations of ileum in control and experimental groups (values expressed as Mean ± SEM)

Sr. No.	Ileum						
	Parameters	Control	Experimental Groups				
			Group I	Group II	Group III	Group IV	Group V
1	Shape of villi	Leaf/finger shaped	Leaf/finger shaped	Leaf/finger shaped	Leaf/finger shaped	Leaf/finger shaped	Leaf/finger shaped
2	Position of villi	Upright	upright	upright	Upright	upright	Upright
3	Height of villi	74.1 ± 8.3	77.6 ± 9.4	76.2± 8.8	74.9±10.4	110.2±11.4	106 ±9.2
4	Inflammatory	Absent	absent	Absent	Absent	absent	Absent
5	Hemorrhage	Absent	absent	Absent	Absent	absent	Absent
6	No. of goblet cell/crypt/HPF	12 ± 1.1	11.2 ± 1.8	11.6 ± 1.2	12.2 ±1.7	11.7 ± 1.1	11.8 ± 1.4
7	No. of columnar cells/crypt/HPF	42.5 ± 3.1	42.8 ± 2.6	41.8 ± 2.9	41.4 ± 2.4	42.7 ± 2.7	43 ± 3.1
8	No. of mitotic cells/crypt/HPF	3.5 ± 0.9	3.1 ± 1.5	3.3 ± 0.8	3.3 ± 0.7	3.2 ± 1.1	3.4 ± 1.2

*P-value < 0.05: significant, **P-value < 0.01: highly significant, ***P-value < 0.001: very highly significant, P-value >0.05: insignificant

On morphometric analysis the numbers of mitotic figures were less in case of experimental groups as compare to control groups. No statistically significant differences in microscopic structure of duodenum, jejunum and ileum were observed between control groups and experimental groups ($p > 0.05$) (table-3, 4 & 5).

DISCUSSION

In the present study, following intragastric administration of curcumin, the intestional length progressively increased upto 16 hours, following which intestinal length began to decrease. After 16 hours of curcumin administration, the effect of curcumin on intestional length diminishes and it became approximately equal to control intestional length (table-1). Ravindranath et al. in their study showed that after administration of 400 mg of curcumin to rats, at 30 minutes 90% of curcumin was found in stomach and small intestine but only 1% was present at 24 hours.[13] That may be the reason that in our study also insignificant results were observed in Group IV & Group V. Srivastava, Srimal (1985) found that in vivo study, pre-treatment of animals with curcumin (200 mg/kg) and ibuprofen (20 mg/kg) for four days reduced the PGE2 content of the exudates by 45 and 61 percent respectively.[14] Rao TS, et. al. (1982) in their experiments on rabbit intestine and guinea pig ileum found that curcumin produces decrease in the resting tone of the rabbit intestine which may indicate increase in length of intestine.[15] Kelley, et. al. (1996) in their study on curcumin found that it inhibits cyclooxygenase-2 (COX-2) expression induced by tumour promoters therefore they concluded that curcumin, like NSAIDS, is a potent anti-inflammatory agent due to inhibition of prostaglandin synthesis.[16] Sanjaya and Aggarwal, (1995) indicated curcumin as a potent inhibitor of NF-kB activation and it down regulates the expression of COX-2 proteins most likely through the down regulation of NF-Kb.[17] Ferreira, Mocada & Vane (1971); Smith & Willis (1971); Aiken & Vanes (1971) in their studies found that Prostaglandin synthesis and release in vitro or in vivo is blocked by NSAIDS.[18-20]

The inherent resting tone of the intestinal smooth muscle is known to be maintained by continuous intramural generation of prostaglandins.[14-16] Curcumin by inhibiting prostaglandin biosynthesis may results in decrease in the resting tone of the intestine and therefore the increase in the length of intestine as observed in our study.

Srinivasan (1953) showed the spasmolytic activity of curcumin.[21] Huang, et. al. (1992) found that sodium curcuminate antagonized the contractions of guinea pig ileum induced by various agonists. It was more active against nicotine-induced contraction on isolated guinea pig ileum.[22] Makhlouf (1994) found that contraction of all smooth muscles, including those of gastrointestinal tract, absolutely depends on the presence of Ca^{2+}. Agonists induced contraction may be related to the release of intracellular Ca^{2+} from the sarcoplasmic stores in addition to its influx, mainly through L-type Ca^{2+} channels from extracellular fluid. Consequently, smooth muscle contraction can be abolished by antispasmodic drugs through the inhibition of Ca^{2+} and its entry or release into the cell.[23]

Turmeric is well known universally for its culinary and medicinal properties. In line with its potential as a gastrointestinal relaxant, Gilan, et. al. (1994) tested its crude extract in isolated rabbit's jejunum and found it to decrease the spontaneous rhythmicity of jejunum.[24] Later Gilani, et. al. (2004) found that the crude extract of turmeric even relaxed the potassium induced contractions in isolated rabbit jejunum. They found that the spasmolytic effect was mediated through the blockade of Ca^{2+} influx.[25]

CONCLUSION

Curcumin increases the length of small intestine, which may be due to decrease in the resting tone of small intestine. This may be the scientific basis of use of curcumin as antispasmodic agent.

ACKNOWLEDGEMENT

Authors are grateful to Himalayan Institute of Medical Sciences, Dehradun for providing

facilities to conduct the study. The authors are grateful to professor Dr. R. K. Sharma and Dr. Rani Gupta, professor and head, Department of Physiology for their kind support and valuable guidance.

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Source of Support: Nil
Conflict of interest: None declared