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The Effect of Curcumin on an Animal Intestinal Ischemia/Reperfusion Model for Bacterial Translocation and Inflammatory Response

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Ischemia/reperfusion (IR) injury of the intestine is a major problem in abdominal pathological condition and is associated with a high morbidity and mortality. The purpose of the study is to investigate the effects of curcumin on the bacterial translocation incidence and inflammatory response in rats submitted to bowel ischemia reperfusion injury. Thirty-two Wistar albino rats with a weight of 200 to 250 g were used in the study. They were randomly divided into 3 groups (n = 10 for each group): sham only operated group(group I); IR group (group II); and IR + curcumin treatment group (group III). Curcumin (curcumin from *Curcuma longa*) 20 mg/kg/day was given orally to the curcumin group. All animals were given 109 *E. Coli* by orogastric intubation 12 hours before sampling. Seventy-two hours after the first operation, mesenteric lymph node and blood samples were obtained and cultured. Blood samples of 2 mL were obtained for a polymerase chain reaction study. A piece of terminal ileum was also sampled for histopathologic examination. Mesenteric lymph node and blood cultures of all control animals were positive for microbiological growth, and polymerase chain reaction results

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were positive in seven of the eight rats. Histopathologically, edema, vasodilatation and inflammatory cell infiltration were found to be less in the other groups in comparison to the control group. Curcumin reduced bacterial translocation in blood, hepatocellular damage, and plasma cytokine levels. Curcumin reduced the incidence of bacterial translocation in intestinal I/R. rats. These results suggest that Curcumin would be clinically useful in the treatment of intestinal I/R injury.

Key words: Bacterial translocation – Curcumin – Ischemia/reperfusion injury – Intestine

The primary functions of the intestine are to absorb nutrients and exclude food debris, bacteria, and their products. Maintenance of these functions relies on the integrity of mucosal barrier of intestine. Gut barrier failure, leading to the passage of viable enteric bacteria and endotoxins across the intestinal mucosal barrier to the mesenteric lymph nodes (MLN) and distant organs, has been termed bacterial translocation (BT).[1,2]

The gastrointestinal tract is a tissue which is highly sensitive to ischemia-reperfusion (IR) injury in the body.[3] The intestinal IR injury is caused by many clinical conditions, including acute mesenteric ischemia, intestinal obstruction, incarcerated hernia, small intestine transplantation, neonatal necrotizing enterocolitis, trauma, and shock.[4–6]

Intestinal I/R induces disruption of the intestinal mucosal barrier, allowing translocation of bacteria and endotoxins from within the bowel into the blood, an event that may initiate a systemic inflammatory response and the secretion and activation of inflammatory mediators, including cytokines and development of remote organ damage and systemic shock.[7,8]

Curcumin is a polyphenol derived from turmeric, which is used as a spice or herbal medicine. It is produced from the root of a plant, *Curcuma longa*. Dried roots of this plant have been used for thousands of years in Asian medicine.[9] Curcumin has been suggested to reduce inflammation which causes bacterial translocation by exhibiting an anti-inflammatory effect.[10]

We aimed to investigate the effects of Curcumin on the BT incidence and inflammatory response in rats submitted to bowel ischemia reperfusion injury.

Materials and Methods

Thirty two Wistar albino rats with a weight of 200 to 250 g were used in the study. All of the experimental protocols were performed according to the guidelines for the ethical treatment of experimental animals.

Animals and experimental protocol

The rats were placed individually in cages and allowed free access to standard rat chow and water before and after the experiments. The animal rooms were windowless and under controlled temperature (22 ± 2°C) and lighting conditions. The animals were made to fast overnight before the experiments, but were given free access to water. They were randomly divided into 3 groups: sham group (group I) was only operated; IR group (group II); and IR + curcumin group (group III) were the treatment groups. They were anesthetized by ketamine HCl 50 mg/mL and xylazine HCl 20 mg/mL applied intramuscularly to the back part of the right leg at 0.25 mL/100 g live weight. The operating field on the abdomen was shaved just before the operation, cleaned with 10% povidone-iodine, and covered in a sterile way but leaving the incision area exposed. Using sterile instruments, a laparotomy was performed through an abdominal midline incision. In sham group (group 1), the rats received a 3-cm medium-length-wise laparotomy, and the small intestine was exposed. Subsequently, the superior mesenteric artery (SMA) was identified and dissected, then the peritoneal cavity was closed. In the IR group, the rats underwent intestinal ischemia for 60 minutes through occlusion of the SMA with a microvascular clamp. The occluding clamp was removed after ischemia for a reperfusion period for 2 hours. Sham and group 2 did not undergo any treatment. The related agent was given to group III for 3 days before sampling. Curcumin (curcumin from *Curcuma longa*; Sigma Aldrich Corp., Darmstadt, Germany) 20 mg/kg/day was given by orogastric tube to the curcumin group. Twelve hours before sampling all animals were given 1 mL of the solution containing *Escherichia coli* 10^9 colony-forming units per milliliter by orogastric intubation. The abdomen was opened again using a

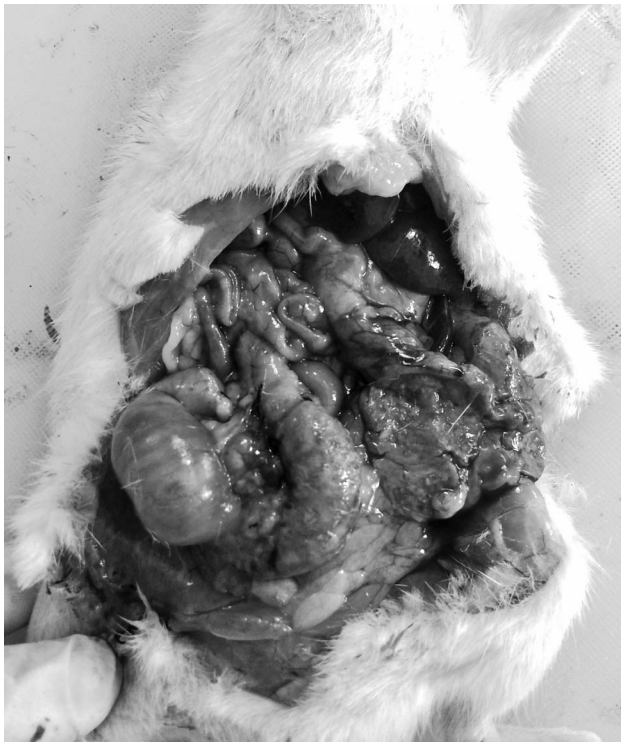

Fig. 1 Macroscopic image in the control group.

sterile technique 72 hours later. For analysis, 5-mL blood samples were drawn from the abdominal aorta, MLN, and blood samples obtained for culture and tissue samples from the terminal ileum were collected (Fig. 1).

Microbiological study

Blood samples for culture were put into culture bottles (Pedi-BacT; bioMérieux, Inc., Crapponne, France) and incubated at 37 °C. Mesenteric lymph nodes samples were put into brain heart infusion agar for culture after crushing and homogenizing with forceps. The polymerase chain reaction of blood samples from test and control animals was performed as described earlier.[11] Briefly, DNA extraction from blood samples was carried out with a commercial DNA extraction kit (Wizard Genomic DNA Purification Kit; Promega, Madison, Wisconsin). The presence of *E. coli* genomic DNA in the extracted samples was sought in PCR assays, and PCR products were electrophoresed on 1, 5% agarose gel (Table 1).

Histopathological study

The terminal ileum samples taken from rats were fixed for 24 hours in 10% formalin. The intestinal segments were divided into pieces 0, 5 × 0, 5 × 0, 5 cm in size and were processed for routine histopathologic examination. The intestinal tissues of each animal were obtained in separate blocks. Sections of 6 to 7 μ, prepared from all tissue samples, were examined by light microscopy. For histopathological evaluation edema, vasodilatation and inflammatory cell infiltration were scored from 0 (slight) to 3 (severe; Tables 2 and 3).

Biochemical examination

Plasma was separated by centrifugation (3000 rpm for 10 minutes at room temperature) for biochemical studies. The activities of alanine aminotransferase (ALT, a specific marker for hepatic parenchymal injury) and aspartate aminotransferase (AST, a nonspecific marker for hepatic injury) in plasma were determined in units per liter using standard autoanalyzer methods (Abbott Aeroset; Abbott Laboratories, Abbott Park, Illinois). The relaparatomy was performed under anesthesia, and their livers were removed for histopathological evaluation, and then they were killed. Alkaline phosphatase (ALP) activity was estimated by the Belfield method.[12] Total bilirubin and γ-glutamyl transferase (GGT) were determined using a diagnostic kit (Diamond Diagnostics, Holliston, Massachusetts) as reported.[13] The enzyme-amplified sensitivity

Table 1 Results from MLN culture, blood culture, and PCR

	MLN culture				Blood culture				PCR			
	Negative		Positive		Negative		Positive		Negative		Positive	
	n	%	n	%	n	%	n	%	n	%	n	%
Group I (n = 10)	8	80	2	20	8	80	2	20	9	90	1	10
Group II (n = 10)	0	0	10	100	0	0	10	100	1	10	9	90
Group III (n = 10)	8	80	2	20	10	100	0	0	9	90	1	10

GI, group I; GII, group II; GIII, group III.

Table 2 Statistical analysis of MLN culture, blood culture, and PCR results

	MLN culture	Blood culture	PCR
GI–GII	**0.006**	**0.006**	**0.01**
GI–GIII	1.00	0.56	1.00
GII–GIII	**0.006**	**0.006**	**0.01**

Fisher's exact test, $P < 0.05$ is significant (significant values are in bold).

Table 3 Statistical analysis of histopathological results

	Edema	Inflammatory cell infiltration	Vasodilatation
Group I–Group II	**0.001**	**0.005**	**0.02**
Group I–Group III	0.56	0.27	0.27
Group II–Group III	**0.001**	**0.02**	**0.02**

Kolmogorov-Smirnov test, $P < 0.05$ is significant (significant values are in bold).

immunoassay method was used for the quantification of tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1β (Diasource; Nivelles, Belgium). The enzyme-linked immunosorbent assay method was used for the measurement of the serum high sensitivity (Hs)–C-reactive protein (CRP) levels (DRG; NJ, USA) (Table 4).

Statistical analysis

Statistical analyses were carried out using a statistical software package (SPSS for Windows 11.5; SPSS, Inc., Chicago, Illinois). The data were expressed as mean ± SD for the biochemical values. Mann Whitney *U* test were used to compare groups variables (biochemical values). Kolmogorov-Smirnov test were used for statistical comparison of the histopathological results. The χ^2 test and Fisher's exact test were used for statistical comparison of the results (MLN culture, blood culture, and PCR results) pertaining to the experimental groups. In the evaluation, $P > 0.05$ was accepted as insignificant and $P < 0.05$ as significant.

Results

The levels of ALT, AST, ALP, GGT, lactate dehydrogenase (LDH), CRP, total bilirubin, IL-1, IL-6 and TNF-α were measured in Table 3. The inflammatory cytokines TNF-α, IL-6, IL-1β, and CRP were increased subsequent to the IR (Table 4). In group III, treatment with curcumin significantly decreased all these cytokines in comparison with the control group. There was no significant difference in terms of serum total bilirubin values among groups and obstructive jaundice was detected in all subjects. In group III, ALT, AST, LDH, and ALP levels were found to be significantly reduced compared to group II ($P = 0.001$, respectively). Furthermore, these enzyme levels were found to be significantly reduced in group I when compared with group II ($P = 0.001$). Levels of TNF-α were detected to be significantly increased in group II when compared with group I ($P = 0.001$). Levels of TNF-α detected in group III were also significantly lower than that of group II and it was significantly different as a statically ($P = 0.001$). Levels or IL-6 levels detected in group III were significantly less than those in group II ($P = 0.001$, respectively). Although the results were lower in group III, they were not statistically significant when compared with group I ($P > 0.05$; Table 4).

Microbiological evaluation showed that all blood and MLN cultures were positive in group II. Nine PCR result were positive in group II. There was 1 positive PCR result in both groups I and III (Table 1).

Table 4 Biochemical results

	Mean ± SD			*P* value		
	Group I	Group II	Group III	GI–GII	GI–GIII	GII–GIII
T-Bil bilirubin	0.21 ± 0.00	0.35 ± 0.06	0.25 ± 0.00	**0.001**	0.15	**0.001**
ALT	41 ± 8	83 ± 18	45 ± 7	**0.001**	0.53	**0.001**
AST	124 ± 9	288 ± 81	128 ± 12	**0.001**	0.27	**0.001**
LDH	1,84 ± 222	3,27 ± 108	2,05 ± 395	**0.001**	0.09	**0.001**
ALP	128 ± 7	274 ± 22	133 ± 11	**0.001**	0.10	**0.001**
TNF-α	1.83 ± 2.76	7.49 ± 1.82	2.05 ± 1.84	**0.001**	0.46	**0.001**
IL–6	31.55 ± 7.35	68.83 ± 11.44	34.67 ± 1.08	**0.001**	0.11	**0.001**
IL–1β	0.44 ± 0.22	1.52 ± 0.79	0.52 ± 0.44	**0.001**	0.42	**0.001**
CRP	30.16 ± 3.44	164.17 ± 31.03	38.31 ± 7.23	**0.001**	0.56	**0.001**

Mann-Whitney *U* test were used, $P < 0.05$ is significant.

The difference between MLN and blood cultures of group II and other groups was significant ($P < 0.05$). The difference between the PCR results of groups I and II was significant ($P < 0.05$) and the difference between groups II and III was also significant ($P < 0.05$; Table 2). As shown in Fig. 1, edema, vasodilatation, and inflammatory cell infiltration were higher in group II than in others (Table 3). Villus height and width, lymphatic dilatation and subepithelial edema were evaluated in terminal ileum sections. In the comparison of villus width, no significant difference was detected among groups, although it was found less frequently in group II ($P > 0.05$). The degree of lymphatic dilatation was observed to be significantly lower in group II than in the others groups. Lymphatic dilatation observed in group II was less than that of group III. Lymphatic dilatation determined in group II was less than that of group I, but this was not statistically significant ($P > 0.05$). In our study, death was observed in 2 rats. The statistical analysis of the histopathological results is shown in Table 3.

Discussion

Bacterial translocation was originally defined and described by Berg and Garlington[14] as the passage of viable bacteria through the intestinal mucosa into the MLN and to other tissues and organs. It has been suggested that gut ischemia/reperfusion induces disruption of the intestinal mucosal barrier, allowing translocation of bacteria and endotoxin from within the bowel into the blood, an event that may initiate a systemic inflammatory response and the secretion and activation of inflammatory mediators, including cytokines.[15]

Bacterial translocation is reported to occur after ischemia-reperfusion injury,[2] thermal injury,[16] hemorrhagic shock,[17] portal hypertension,[18] pancreatitis,[19] intestinal obstruction,[20] chirrosis,[21] obstructive jaundice,[22] and Crohn's disease.[23]

The intestinal mucosa is a major barrier preventing the systemic spread of the colonizing bacteria from the gut.[24] Bacterial translocation is suggested to be an important factor contributing to the development of sepsis.[25,26]

Curcumin, a widely used orange-yellow curry pigment from turmeric (*Curcuma longa*), has been designated to be a forceful anti-inflammatory, anticancer and antioxidant agent, and is under preclinical trial for cancer prevention and anti-inflammation.[27,28] Lately, curcumin was shown to inhibit the production of nitric oxide (NO) and the expression of inducible NO synthase (iNOS) in mesenteric ischemia-reperfusion injury and erectile dysfunction.[29,49] Moreover, curcumin has been shown to have positive effects on inflammatory damage and intestinal reperfusion injury in a recent experimental study by Karatepe *et al*.[30] In the study performed by Shen *et al*,[31] curcumin was shown to increase expression of antioxidant biomolecules and reduce neutrophil infiltration and reactive oxygen metabolites after ischemia-reperfusion injury in the liver. In our study, intestinal reperfusion injury of group III were lower than II and it was statistically significant ($P = 0.001$).

Curcumin is potentially safe medication for maintaining remission in patients with quiescent ulcerative colitis. Two early-phase trials conducted by Holt[24] and Hanai[32] have shown it to be well tolerated by patients with colitis and can lead to reduced symptoms and inflammatory markers. Curcumin regulates the activity of macrophages and natural killer cells.[33] This may be related to downregulation of NO and the cytokine response. It enhances the phagocytosis by macrophages and reduces the ability to produce reactive oxygen species.[34] Production of TNF-α and NO is inhibited by curcumin in vivo, consequently reducing tissue damage.[35] The promising outcomes from animal models of inflammatory bowel disease (IBD) treated with curcumin have so far been supported by early clinical trial data.[32,36] Bacterial translocation is precipitated by bacterial overgrowth disturbing the normal ecologic balance,[37] host immune dysfunction inciting pro and anti-inflammatory cytokines balance,[38] and mucosal barrier dysfunction, favoring oxidants release.[39]

Many agents used to prevent BT and glutamin, enisoprost, vitamins C and E, zinc, melatonin, levamisole, tungsten supplemented diet, and probiotic *Lactobacillus plantarum* 299V are shown to decrease BT.[40,41] It has been considered that the beneficial effects of curcumin are mediated by its antioxidant defense ability and the scavenging of free radicals; moreover, curcumin is at least 10 times more active as an antioxidant than vitamin E.[42] Curcumin attenuates prevents circulatory failure in rats with endotoxemia by inhibiting the release of TNF-α.[34] Tumor necrosis factor alpha is a multifunctional cytokine produced primarily by activated monocytes and macrophages and plays a crucial role in the initiation and continuation of mucosal inflammation and immunity.[43,44] In our study, we detected a statistically significant difference in the treatment and control groups in terms of TNF-α ($P = 0.001$; Table 4).

During the last 20 years, the PCR is used to detect the genetic material of many infectious agents in various milieus at high sensitivity.[45] Measures of BT are blood cultures, MLN cultures, bacterial scintigraphy with 99mTc-labelled *E. Coli* and PCR.[45] Polymerase chain reaction is a superior way of determining BT.[11] Cytokines like IL-1β and IL-6 lead to pro-inflammatory and inflammatory changes and the rapid immune response, enabling the elimination of the pathogens.[46] Interleukin-1β is known to be an effective inhibitor of a number of molecules leading to oxidative injury caused by the generation of free radicals such as lipoxygenase, cyclooxygenase, xanthine oxidase, xanthine dehydrogenase, nitric oxide synthase, and TNF-α.[29,47]

In our I/R model, the SMA of rats was clamped for 60 minutes and the rats were killed after 72 hours. Mesenteric lymph nodes and blood were then cultured quantitatively. Almost all MLN had positive cultures and grew significantly great numbers of enteric bacteria, spread to the blood, liver, and spleen in I/R-PN group. The most common bacterium discovered from solid viscera was *E. coli*; other species included enterococcus, pseudomonas, proteus, and staphylococcus.

Moreover, the levels of TNF-α, IL-1β, IL-6, and CRP were decreased in serum treatment group according to the control group (Table 4). The translocation of the *E. coli* from extra-intestinal sites was examined in the study in order to obtain direct support for using curcumin that protects the intestinal barrier (Table 2). In this study, increased serum levels of TNF-α, IL-1β, IL-6, and IL-10 reflected the ischemia/reperfusion injury, as demonstrated by other in vivo trials.[26,28,48] In the rats treated with curcumin, a significantly different cytokine response was observed, which was characterized by decreased production of TNF-α, IL-1β, and IL-6. As shown in the present study, bowel ischemia and reperfusion promoted bacteria translocation. In addition, when compared with the sham, this phenomenon was significantly higher for MLN and serum in all other groups.

Conclusion

Curcumin reduced the incidence of BT in intestinal I/R. rats. Also, curcumin was observed to reduce serum cytokine levels in comparison with the control group. However, more extensive comparative experimental and clinical studies are required before the clinical use of curcumin for this purpose.

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