

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

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 guide-

lines 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 ($22 \pm 2^\circ\text{C}$) 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 relaparotomy 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).

immunoassay method was used for the quantification of tumor necrosis factor (TNF)- α , interleukin (IL)-6, and IL-1 β (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 \pm 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

Table 4 Biochemical results

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

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

Table 3 Statistical analysis of histopathological results

	Inflammatory cell		
	Edema	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).

TNF- α were measured in Table 3. The inflammatory cytokines TNF- α , IL-6, IL-1 β , 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).

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 Garlington¹⁴ 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 cirrhosis,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, anti-cancer 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 Holt²⁴ and Hanai³² 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-1 β and IL-6 lead to pro-inflammatory and inflammatory changes and the rapid immune response, enabling the elimination of the pathogens.⁴⁶ Interleukin-1 β 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-1 β , 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-1 β , 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-1 β , 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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References

1. MacFie J, O'Boyle C, Mitchell CJ, Buckley PM, Johnstone D, Sudworth P. Gut origin of sepsis: a prospective study investigating associations between bacterial translocation, gastric microflora, and septic morbidity. *Gut* 1999;**45**(2):223–228
2. Sen V, Uluca U, Ece A, Güneş A, Zeytun H, Arslan S *et al.* Role of Ankaferd on bacterial translocation and inflammatory response in an experimental rat model of intestinal obstruction. *Int J Clin Exp Med* 2014;**15**(7):2677–2686
3. Mojzis J, Hviscova K, Germanova D, Bukovicova D, Mirossay L. Protective effect of quercetin on ischemia/reperfusion-induced gastric mucosal injury in rats. *Physiol Res* 2001;**50**(5):501–506
4. Mallick IH, Yang W, Winslet MC, Seifalian AM. Ischemia-reperfusion injury of the intestine and protective strategies against injury. *Dig Dis Sci* 2004;**49**(9):1359–1377
5. Guneli E, Cavdar Z, Islekel H, Sarioglu S, Erbayraktar S, Kiray M *et al.* Erythropoietin protects the intestine against ischemia/reperfusion injury in rats. *Mol Med* 2007;**13**(9-10):509–517
6. Teke Z, Kabay B, Aytekin FO, Yenisey C, Demirkan NC, Sacar M *et al.* Pyrrolidine dithiocarbamate prevents 60 minutes of warm mesenteric ischemia/reperfusion injury in rats. *Am J Surg* 2007;**194**(2):255–262
7. Grant D, Wall W, Mimeault R, Zhong R, Ghent C, Garcia B *et al.* Successful small-bowel/liver transplantation. *Lancet* 1990; **335**:181–184
8. Leaphart CL, Tepas JJ 3rd. The gut is a motor of organ system dysfunction. *Surgery* 2007;**141**:563–569
9. Afshariani R, Farhadi P, Ghaffarpasand F, Roozbeh J. Effectiveness of topical curcumin for treatment of mastitis in breastfeeding women: a randomized, double-blind, placebo-controlled clinical trial. *Oman Med J.* 2014;**29**(5):330–334
10. Gülçubuk A, Sönmez K, Gürel A, Altunatmaz K, Gürler N, Aydın S *et al.* Pathologic alterations detected in acute pancreatitis induced by sodium taurocholate in rats and therapeutic effects of curcumin, ciprofloxacin and metronidazole combination. *Pancreatology* 2005;**5**(4-5):345–353
11. Kazez A, Sağlam M, Doymaz Z, Bulut Y, Aşçı Z. Detection of bacterial translocation during intestinal distension in rats using the polymerase chain reaction. *Pediatr Surg Int* 2001;**17**:624–627

12. Belfield A, Goldberg DM. Revised assay for serum phenyl phosphatase activity using 4-amino-antipyrine. *Enzyme* 1971;**12**:561–573
13. Henry RJ. *Clinical Chemistry, Principles and Techniques*. 2nd ed. New York: Harper and Row, 1974
14. Berg R, Garlington AW. Translocation of certain indigenous bacteria from the gastrointestinal tract to the mesenteric lymph-nodes and the other organs in a gnotobiotic mouse model. *Infect Immunol* 1979;**23**:403–411
15. Caty MG, Guice KS, Oldham KT, Remick DG, Kunkel SI. Evidence for tumor necrosis factor-induced pulmonary injury after intestinal ischemia reperfusion injury. *Ann Surg* 1990;**212**(6):694–700
16. Chen LW, Chang WJ, Chen P, Hsu CM. Commensal microflora induce host defense and decrease bacterial translocation in burn mice through toll-like receptor 4. *J Biomed Sci*. 2010;**17**:48
17. Wang P, Wei X, Li Y, Li J. Influences of intestinal ligation on bacterial translocation and inflammatory response in rats with hemorrhagic shock: implications for damage control surgery. *J Invest Surg* 2008;**21**(5):244–254
18. Neugebauer H, Hartmann P, Krenn S, Glück T, Schölmerich J, Straub R *et al*. Bacterial translocation increases phagocytic activity of polymorphonuclear leucocytes in portal hypertension: priming independent of liver cirrhosis. *Liver Int*. 2008;**28**(8):1149–1157
19. Berkem H, Yüksel BC, Berkem R, Yıldız SY, Gündoğdu K, Özel IH *et al*. The effects of intravenous glutamine on bacterial translocation and intestinal morphology in experimental pancreatitis. *Turk J Med Sci* 2008;**38**(2):127–132
20. Gatt M, Reddy BS, Macfie J. Review article: bacterial translocation in the critically ill—evidence and methods of prevention. *Aliment Pharmacol Ther* 2007;**25**(7):741–757
21. Veal N, Audubertau H, Lemarie C, Oberti F, Calès P. Effects of octreotide on intestinal transit and bacterial translocation in conscious rats with portal hypertension and liver fibrosis. *Dig Dis Sci* 2001;**46**(11):2367–2373
22. Kapan M, Tekin R, Onder A, Firat U, Evliyaoglu O, Taskesen F *et al*. Thymoquinone ameliorates bacterial translocation and inflammatory response in rats with intestinal obstruction. *Int J Surg* 2012;**10**(9):484–488
23. Zhao Y, Zhang S, Jiang L, Jiang J, Liu H. Preventive effects of *Schistosoma japonicum* ova on trinitrobenzenesulfonic acid-induced colitis and bacterial translocation in mice. *J Gastroenterol Hepatol* 2009;**24**(11):1775–1780
24. Holt PR, Katz S, Kirshoff R. Curcumin therapy in inflammatory bowel disease: a pilot study. *Dig Dis Sci* 2005;**50**(11): 2191–2193
25. Deriy LV, Beno DW, Uhing MR, Jiyamapa-Serna VA, Kimura RE. Splenectomy ablates endotoxin-induced IFN gamma response in rats. *Shock* 2002;**17**(4):312–315
26. Oguz A, Kapan M, Onder A, Kilic E, Gumus M, Basarali MK *et al*. The effects of curcumin on the liver and remote organs after hepatic ischemia reperfusion injury formed with Pringle manoeuvre in rats. *Eur Rev Med Pharmacol Sci*. 2013;**17**(4):457–466
27. Strimpakos AS, Sharma RA. Curcumin: preventive and therapeutic properties in laboratory studies and clinical trials. *Antioxid Redox Signal* 2008;**10**(3):511–545
28. Fan Z, Jing H, Yao J, Li Y, Hu X, Shao H *et al*. The protective effects of curcumin on experimental acute liver lesion induced by intestinal ischemia-reperfusion through inhibiting the pathway of NF- κ B in a rat model. *Oxid Med Cell Longev* 2014;**2014**:191624
29. El-Bassossy HM, Hassan N, Zakaria MN. Heme oxygenase-1 alleviates vascular complications associated with metabolic syndrome: Effect on endothelial dependent relaxation and NO production. *Chem Biol Interact* 2014;**28**:223C:109–115
30. Karatepe O, Gulcicek OB, Ugurlucan M, Adas G, Battal M, Kemik A *et al*. Curcumin nutrition for the prevention of mesenteric ischemia-reperfusion injury: an experimental rodent model. *Transplant Proc* 2009;**41**(9):3611–3616
31. Shen SQ, Zhang Y, Xiang JJ, Xiong CL. Protective effect of curcumin against liver warm ischemia/reperfusion injury in rat model is associated with regulation of heat shock protein and antioxidant enzymes. *World J Gastroenterol* 2007;**13**(13): 1953–1961
32. Hanai H, Iida T, Takeuchi K, Watanabe F, Maruyama Y, Andoh A *et al*. Curcumin maintenance therapy for ulcerative colitis: randomized, multicenter, double-blind, placebo-controlled trial. *Clin Gastroenterol Hepatol* 2006;**4**(12):1502–1506
33. Bhaumik S, Jyothi MD, Khar A. Differential modulation of nitric oxide production by curcumin in host macrophages and NK cells. *FEBS Lett* 2000;**483**(1):78–82
34. Joe B, Lokesh BR. Role of capsaicin, curcumin and dietary n-3 fatty acids in lowering the generation of reactive oxygen species in rat peritoneal macrophages. *Biochim Biophys Acta* 1994;**1224**(2):255–263
35. Sharma S, Kulkarni SK, Agrewala JN, Chopra K. Curcumin attenuates thermal hyperalgesia in a diabetic mouse model of neuropathic pain. *Eur J Pharmacol* 2006;**536**(3):256–261
36. Larmonier CB, Midura-Kiela MT, Ramalingam R, Laubitz D, Janikashvili N, Larmonier N *et al*. Modulation of neutrophil motility by curcumin: implications for inflammatory bowel disease. *Inflamm Bowel Dis* 2011;**17**(2):503–515
37. Nieuwenhuijs VB, Verheem A, van Duijvenbode-Beumer H, Visser MR, Verhoef J, Gooszen HG *et al*. The role of interdigestive small bowel motility in the regulation of gut microflora, bacterial overgrowth, and bacterial translocation in rats. *Ann Surg* 1998;**228**(2):188–193
38. Lane JS, Todd KE, Lewis MP, Gloor B, Ashley SW, Reber HA *et al*. Interleukin-10 reduces the systemic inflammatory

- response in a murine model of intestinal ischemia/reperfusion. *Surgery* 1997;**122**(2):288–294
39. Choudhry MA, Fazal N, Goto M, Gamelli RL, Sayeed MM. Gut associated lymphoid T cell suppression enhances bacterial translocation in alcohol and burn injury. *Am J Physiol Gastrointest Liver Physiol* 2002;**282**(6):G937–G947
40. Gandhimathi C, Venugopal JR, Bhaarithy V, Ramakrishna S, Kumar SD. Biocomposite nanofibrous strategies for the controlled release of biomolecules for skin tissue regeneration. *Int J Nanomedicine* 2014;**9**:4709–4722
41. Çetinkaya Z, Ülger H, Akkus MA, Doğru O, Çifter Ç, Doymaz MZ *et al.* Influence of some substances on bacterial translocation in the rat. *World J Surg* 2002;**26**:9–12
42. Wei W, Hua G, Zhaoru L, Hong L, Zhangzhi Z. Effect of curcumin on rats/mice with diabetic nephropathy: a systematic review and Meta-analysis of randomized controlled trials. *J Tradit Chin Med* 2014;**34**(4):419–429
43. Gurleyik E, Coskun O, Ustundag N, Ozturk E. Prostaglandin E1 maintains structural integrity of intestinal mucosa and prevents bacterial translocation during experimental obstructive jaundice. *J Invest Surg* 2006;**19**(5):283–289
44. Adams DH, Lloyd AR. Chemokines: leucocyte recruitment and activation cytokines. *Lancet* 1997;**349**(9050):490–495
45. Lloyd CM, Dorf ME, Proudfoot A, Salant DJ, Gutierrez-Ramos JC. Role of MCP-1 and RANTES in inflammation and progression to fibrosis during murine crescentic nephritis. *J Leukoc Biol* 1997;**62**(5):676–680
46. Kane TD, Johnson SR, Alexander JW, Babcock GF, Ogle CK. Detection of intestinal bacterial translocation using PCR. *J Surg Research* 1996;**63**(1):59–63
47. Bethea JR, Chung IY, Sparacio SM, Gillespie GY, Benveniste EN. Interleukin-1 beta induction of tumor necrosis factor-alpha gene expression in human astrogloma cells. *J Neuroimmunol* 1992;**36**(2-3):179–181
48. Fujino Y, Suzuki Y, Kakinoki K, Tanioka Y, Ku Y, Kuroda Y. Protection against experimental small intestinal ischaemia-reperfusion injury with oxygenated perfluorochemical. *Br J Surg* 2003;**90**(8):1015–1020
49. Zaahkoug AM, Abdel Aziz MT, Rezaq AM, Atta HM, Fouad HH, Ahmed HH *et al.* Efficacy of a novel water-soluble curcumin derivative versus sildenafil citrate in mediating erectile function. *Int J Impot Res* 2015;**27**(1):9–15