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Original Article

Protective effect of Curcumin on chemotherapy-induced intestinal dysfunction

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Abstract: Objective: Chemotherapy is one of most important treatments for human cancers. However, side effects such as intestine dysfunction significantly impaired its clinical efficacy. This study aimed to investigate the protective effect of Curcumin on chemotherapy-induced intestinal dysfunction in rats. Methods: Sixty healthy Wistar rats were randomly divided into control group (normal saline), 5-FU group and 5-FU+Curcumin group. The weight, serum level of endotoxin, DAO and D-lactate were determined. The pathological change of intestinal mucosa structure was studied under light microscopy and electron microscopy. The expression of Bax, Bcl-2 and Caspase-3 were assessed by immunohistochemical staining. Results: The Curcumin intragastrically administrated obviously reduced 5-FU-induced weight-loss. 5-FU induced dramatic increase of serum endotoxin, D-lactate and D-Amino-Acid Oxidase (DAO) that were significantly reversed by Curcumin treatment. Meanwhile, 5-FU-induced-damage to intestinal mucosa structure was markedly recovered by Curcumin. The expression of Bax and Caspase-3 were dramatically increased after 5-FU treatment ($p<0.01$) and Curcumin treatment significantly reduced Bax expression ($p<0.05$) but had only a moderate effect on reducing caspase-3 expression ($p>0.05$). Interestingly, Bcl-2 expression was low in control group but increased after 5-FU treatment ($p>0.05$) and Curcumin treatment further stimulated Bcl-2 expression ($p<0.05$). Conclusions: Curcumin can significantly reverse chemotherapy-induced weight-loss, increase of serum endotoxin, D-lactate and DAO and damage to intestinal mucosa structure. Curcumin also reduced the expression of pro-apoptotic Bax but stimulated anti-apoptotic Bcl-2 to attenuate 5-FU-induced apoptosis of intestinal epithelial cells. The clinical administration of Curcumin may improve chemotherapy-induced intestinal dysfunction, thus increasing the clinical efficacy of chemotherapy.

Keywords: Curcumin, chemotherapy-induced, intestinal dysfunction, Bax, Bcl-2, 5-FU, ultrastructures

Introduction

Despite rapid advances in the development of anti-cancer treatments, chemotherapy remains one of most important approaches in the treatment of many if not all human cancers [1]. Chemotherapy is the main adjuvant therapy after or before surgery and primary therapy of advanced malignant tumors. The side effects are the major clinical concern and dose-limiting factor to affect the clinical efficacy of chemotherapy. Among them, myelosuppression and digestive dysfunction are the most common side effects eventually affect further clinical managements. Recently, myelosuppression can be successfully prevented or managed with the development in producing recombinant myostimulating factors such as GM-CSF (granulocyte-macrophage colony stimulating factor) or G-CSF (granulocyte colony stimulating factor) and the prophylactic application of high efficient antibiotics. However, digestive dysfunction remains the major challenge for medical oncologists to improve the chemotherapy efficacy and the quality-of-life of cancer patients undertaking chemotherapy [2].

Due to its high turnover rate, the epithelium of gastrointestinal tract is susceptible to chemotherapy-induced damage, leading to the des-

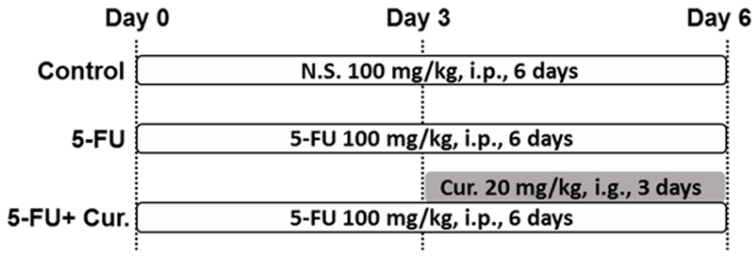


Figure 1. The experiment design. 5-FU or normal saline (N.S.) were given intraperitoneally (i.p.) from Day 1 to Day 6 and Curcumin (Cur.) were given by intragastric administration (i.g.).

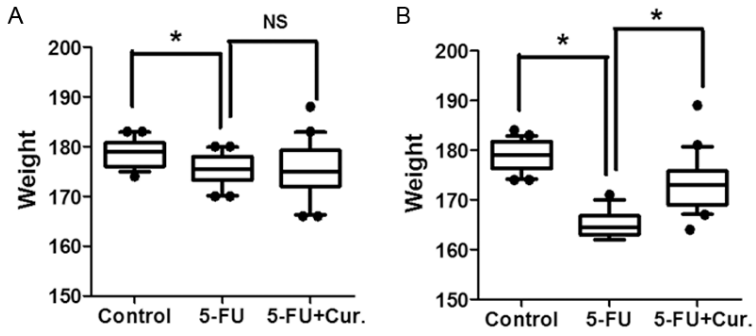


Figure 2. Weight changes of rats in three groups. Weights of rats in three groups were measured at Day 3 (A) and Day 6 (B). The difference were analyzed by ANOVA test. The asterisks indicate statistical significance ($p<0.05$) while ns indicates no significant difference ($p>0.05$).

truction of intestinal mucosa barrier (IMB) and subsequent clinical manifestations such as mild fever, nausea, diarrhea, vomiting and anorexia [3-6]. Therefore, agents or approaches that can maintain the function and structural integrity of IMB will prevent or alleviate chemotherapy-induced intestinal dysfunction [7]. Recently, the combinations of chemotherapy and traditional Chinese medicines (TCMs) or natural products have recently emerged as a new method of cancer therapy, relying on the capacity of TCMs to trigger cell death with few side effects [8-10]. In addition, TCMs were found to have intriguing pharmacologic effects and therapeutic advantages for managing intestinal dysfunction. Isolated from the rhizomes of the plant Curcuma Longa, Curcumin is the main active component of ginger and was found to have many biological effects such as anti-inflammation, anti-oxidization, free radical removal, and anti-cancer [11, 12]. In this study, we evaluated the protective effect of Curcumin on intestinal dysfunction and IMB injury induced by 5-fluorouracil (5-FU) in rats.

Materials and methods

Reagents

Curcumin and 5-fluorouracil (5-FU) were bought from Dawen Bio-Technology (Hangzhou, China), and Jinyao Bio-Technology (Tianjin, China), respectively. ELISA assay kits were bought from Huamei Bio-Technology (Wuhan, China). All primers were synthesized by Huada Gene (Beijing, China).

Animals and experiment design

Sixty healthy Wistar rats weighing about 200 g were purchased from the Laboratory Animal Center (Zhejiang Chinese Medical University, Hangzhou, China) and randomly divided into 3 groups: Control group, 5-FU, and 5-FU+Curcumin group. The treatments of animals in different groups were shown in **Figure 1**. The weight of rats was recorded before and after treatment. Blood samples were drawn on Day 2, 4 and 6. Tissues were collected after the termination of the animal experiment.

ELISA (enzyme-linked immunosorbent assay)

The serum level of endotoxin, D-Amino-Acid Oxidase (DAO) and D-lactate were measured by ELISA. All blood samples were centrifuged with 3,000 rpm for 10 min and the supernatant were stored in -80°C refrigerator. The ELISA were performed according to the manufacturer's protocol.

Tissue morphology analysis

Specimens about 3 cm of ileum were obtained just 3 cm above the ileoceacum. All tissues were fixed in 10% neutral formalin and embedded in paraffin, then sectioned and stained with Hematoxylin-Eosin. The histomorphology changes of intestinal mucosa were evaluated under light microscopy. For ultrastructural morphology analysis, ileum fragments from three rats of each group were fixed by 2.5% glutaral-

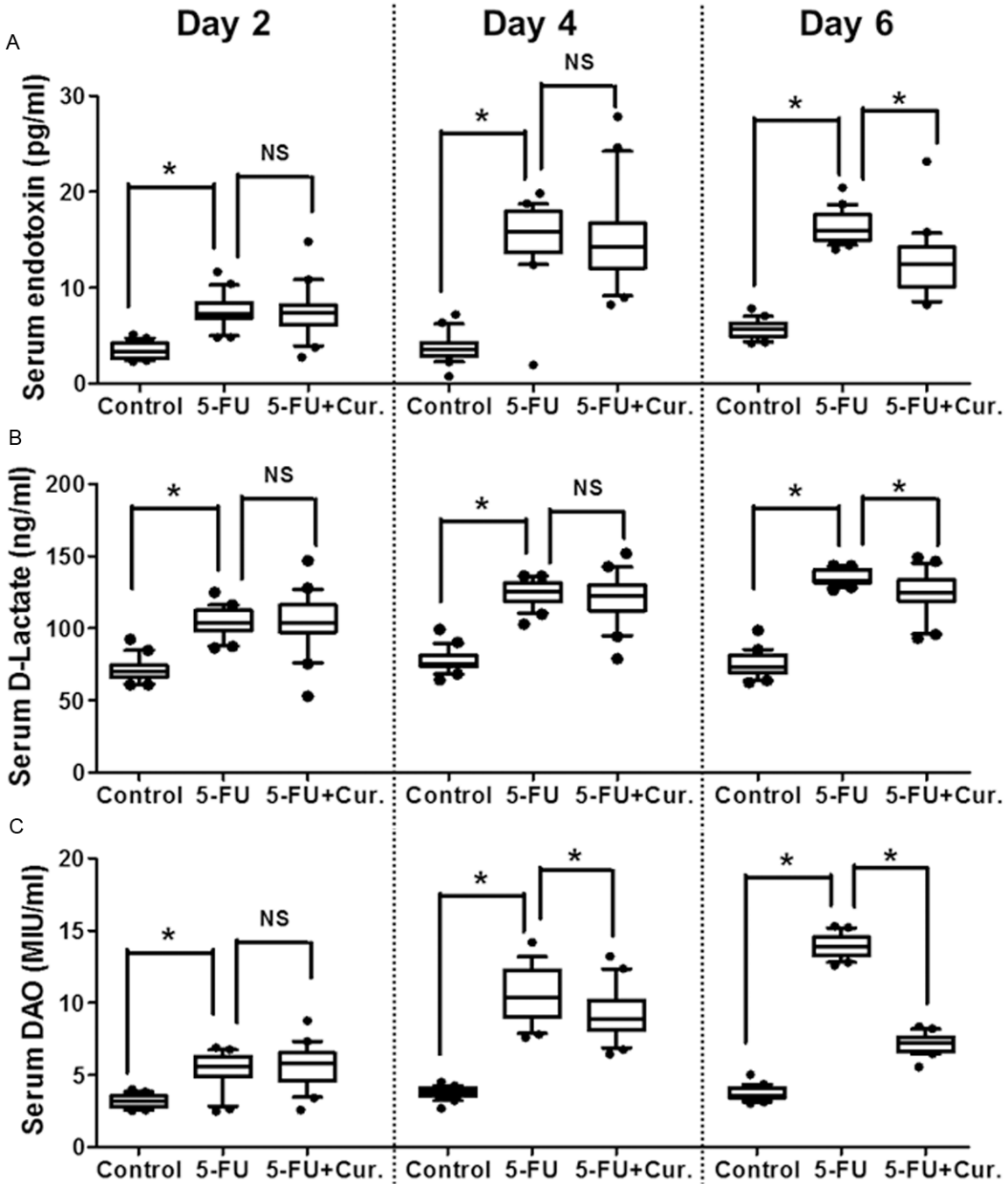


Figure 3. Effects of curcumin on serum biomarkers. The serum level of endotoxin (A), D-lactate (B) and DAO (C) at Day 2, Day 4 and Day 6 were analyzed by ELISA. The difference were analyzed by ANOVA test. The asterisks indicate statistical significance ($p<0.05$) while ns indicates no significant difference ($p>0.05$).

dehyde and examined under transmission electron microscopy.

Immunohistochemistry staining

The expression of Bax, Bcl-2 and Caspase-3 were determined by immunohistochemistry (IHC) staining according to previously described [13]. Briefly, following antigen retrieval, the sections were blocked with normal goat serum (Dako, Glostrup, Denmark) and then incubated with primary antibodies overnight at 4°C. The detection of the antigen-antibody complex was performed using a goat anti-rabbit secondary

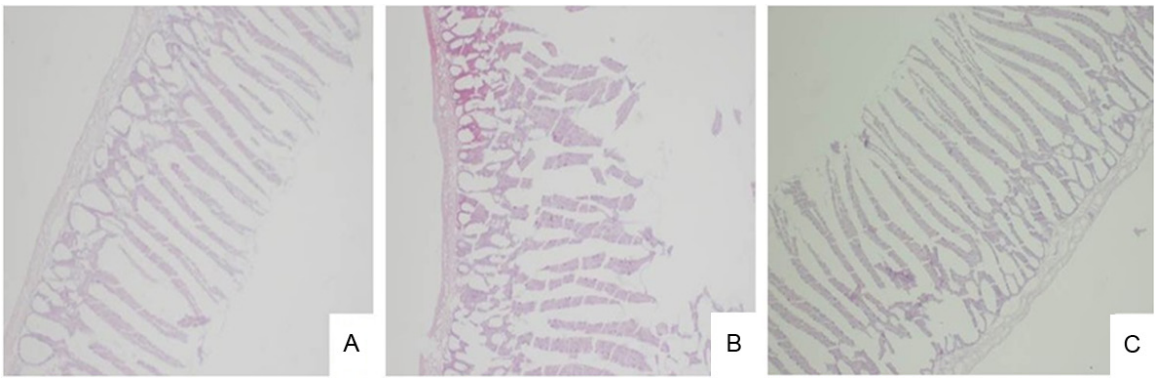


Figure 4. Histological analysis of the ileum mucosa. The small intestine of rats in three groups were analyzed by Hematoxylin-Eosin (HE) staining. The representative figures were shown (× 100). A: Control; B: 5-FU and C: 5-FU+Cur.

antibody and the Streptavidin-HRP Systems kit (Dako).

Results

Effect of Curcumin on behavior changes of rats treated with 5-FU

On Day 3 (**Figure 1**), rats in 5-FU and 5-FU+ Curcumin groups was listless, moved slowly, and presented with liquid stools. One day after the treatment of Curcumin (Day 4), rats in 5-FU+Curcumin group had less diarrhea, better spirit and appetite while rats in 5-FU group had no change. At Day 6, rats of 5-FU group still presented severe diarrhea whereas rats of other groups had no symptoms at all.

There was no significant difference in weight of rats from different groups at the baseline (data not shown). On Day 3, the weight of rats in Control, 5-FU and 5-FU+Cur Groups were 178.0±2.6 g, 175.4±6.4 g and 175.8±3.5 g, respectively (**Figure 2A**). The weight of rats with 5-FU treatment were significantly decreased (Control vs 5-FU, $p<0.05$; Control vs 5-FU+Cur., $p<0.05$). There is no statistical difference between the weight of rats in 5-FU and 5-FU+Curcumin groups (5-FU vs 5-FU+Cur., $p>0.05$). At Day 6, the weight of rats in three groups was 180.3±2.1 g, 165.2±2.3 g and 173.0±6.5 g, respectively (**Figure 2B**). The weight of rats in 5-FU group was still significantly lower than the weight of rats in the control group (Control vs 5-FU, $p<0.01$). However, the weight of rats in 5-FU+Curcumin group was significantly increased (5-FU vs 5-FU+Cur., $p< 0.01$).

Effect of Curcumin on serum markers

All of these observations indicate that the administration of Curcumin could improve 5-FU-induced intestinal dysfunction. To prove this assumption, we determined the serum level of endotoxin, D-Lactate and D-Amino-Acid Oxidase (DAO) in rats before and after the treatment of 5-FU and Curcumin. As shown in **Figure 3A**, serum endotoxin level in 5-FU-treated rats started to increase at Day 2 (Control vs 5-FU, $p<0.05$) and maintain at high levels through the experiment (Day 4 and Day 6, Control vs 5-FU, $p<0.01$). Serum endotoxin levels were significantly decreased after three-day treatment of Curcumin (Day 6, 5-FU vs 5-FU+Cur., $p<0.01$) although one-day Curcumin treatment failed to reverse 5-FU-induced increase of endotoxin (Day 4, 5-FU vs 5-FU+Cur., $p>0.05$). Similarly, 5-FU treatment significantly increased serum level of D-Lactate that was remarkably rescued by the three-days but not one-day treatment of Curcumin (Day 4, 5-FU vs 5-FU+Cur., $p>0.05$; Day 6, 5-FU vs 5-FU+Cur., $p<0.01$) (**Figure 3B**). Furthermore, 5-FU treatment dramatically increased serum level of DAO that was significantly rescued by both one-day and three-days treatment of Curcumin (Day 4, 5-FU vs 5-FU+Cur., $p<0.05$; Day 6, 5-FU vs 5-FU+Cur., $p<0.01$) (**Figure 3C**).

Effect of Curcumin on the intestinal morphology

We further analyzed the structure of small intestine in rats of different groups by microscopic examination. For small intestinal of rats in the control group, the mucosa had uniform

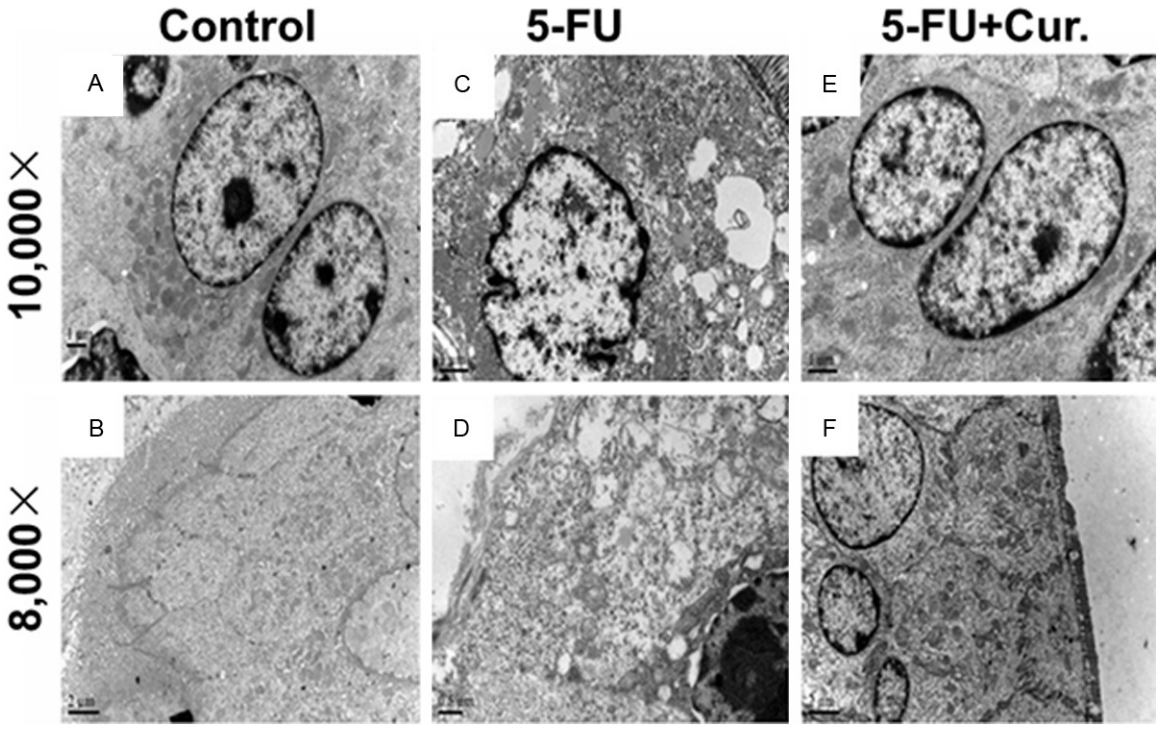


Figure 5. Ultrastructural analysis of Intestinal tissues. The ultrastructures of small intestines were analyzed by electron microscopy. The representative figures were shown. A and B: Control; C and D: 5-FU; E and F: 5-FU+Cur.

thickness and the villi arranged orderly with uniform length (**Figure 4A**). In addition, surface epitheliums were continuous and intact without the infiltration of lymphocytes or other inflammatory cells. In contrast, the small intestine of rats in 5-FU group showed obvious mucosa atrophy and villi loss with the degeneration and necrosis of epithelium cells and remarkable infiltration of inflammatory cells mainly lymphocytes (**Figure 4B**). After the administration of Curcumin, mucosa morphology was significantly improved compared with 5-FU group (**Figure 4C**). The mucosa was thicker, better organized and infiltrated with less inflammatory cells.

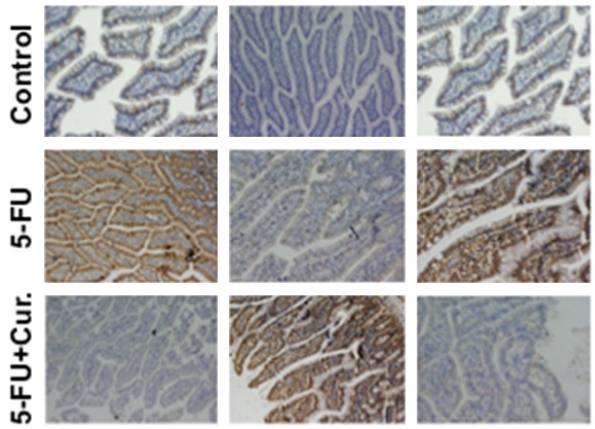
Effect of Curcumin on the ultrastructure of small intestine

Ultrastructural examination by electron microscopy revealed that epithelial cells from the small intestine of rats in the control group were oval with large nucleus, little cytoplasm and well-distributed chromatin (**Figure 5A** and 5**B**). In addition, the villi arranged orderly and are dense with clear connections. The mitochondria were oval with clear cristae and other substructures. All other organelles such as endoplasmic reticulum (ER) are with clear integrity. In contrast, the epithelial cells from rats in 5-FU group showed obvious structural destructions. The cell volume was shrunk with deformed nucleus and the chromatin was marginalized and became lumpy. The intestinal villi were shortened and disturbed even broken. Various organelles had edema and degeneration such as the dilation even the vacuolation of the ERs and turgidity of the mitochondria (**Figure 5C** and **5D**). The intestinal structure in rats of the 5-FU+Curcumin group was markedly restored (**Figure 5E** and **5F**). Intestinal mucosa cells were intact and well organized. The villi were arranged orderly.

Effect of Curcumin on gene expression in small intestine

We further determined the expression of some apoptosis-related genes in the small intestine (**Figure 6A**). The expression of Bcl-2, Bax and Caspase-3 in three group were summarized in **Figure 6B**. Our results indicated that the expression of Bax and Caspase-3 were dramatically increased after 5-FU treatment (Bax positive rate: 30% in Control group, 85% in 5-FU group, Chi-square test, $p<0.01$; Caspase-3 positive rate: 25% in Control group, 80% in

A



B

Effect of Curcumin on gene expression

		Control	5-FU	5-FU+Cur.
Bax	-	14	3	9
	+	6	17	11
Bcl-2	-	18	13	6
	+	2	7	14
Caspase-3	-	15	4	8
	+	5	16	12

Figure 6. Effect of Curcumin on the expression of Bax, Bcl-2 and Caspase-3. The expression of Bax, Bcl-2 and Caspase-3 were determined by immunohistochemical staining. The representative figures were shown in A and the staining results were summarized in B.

5-FU group, Chi-square test, $p<0.01$). Curcumin treatment significantly reduced the expression of Bax (Bax positive rate: 55% in 5-FU+Cur. group, 5-FU vs 5-FU+Cur. Chi-square test, $p<0.05$) but had only a moderate effect on reducing caspase-3 expression (Caspase-3 positive rate: 60% in 5-FU+Cur. group, 5-FU vs 5-FU+Cur. Chi-square test, $p>0.05$). Interestingly, Bcl-2 expression was lower in control group but increased after 5-FU treatment (Bcl-2 positive rate: 10% in Control group, 35% in 5-FU group, Chi-square test, $p>0.05$) and Curcumin treatment further stimulated the expression of Bcl-2 (Bcl-2 positive rate: 70% in 5-FU+Cur. group, 5-FU vs 5-FU+Cur. Chi-square test, $p<0.05$).

Discussion

In this study, we found that Curcumin significantly reversed chemotherapy-induced weight-loss, increase of serum endotoxin, D-lactate and DAO and destruction intestinal mucosa structure. Therefore, the administration of Curcumin may improve chemotherapy-induced intestinal dysfunction, thus increasing the clinical efficacy of chemotherapy.

Cytotoxic chemotherapy frequently induced the injury of intestinal epithelium that acts as an important mechanical barrier to prevent local or systemic invasion by microorganisms or endotoxins [14]. Infection can also exacerbate mucosa injury after cancer treatment. For example, latent herpes simplex virus type 1 (HSV-1) is frequently reactivated in HSV-seropositive patients, leading to stomatitis. Thus, antiviral or antibacterial prophylaxis will be beneficial to minimize chemotherapy-induced intestinal dysfunction and facilitate optimal delivery of the antineoplastic regimen. In addition, treatments to prevent or alleviate mucosa injury with non-antibiotics could be helpful to manage chemotherapy-induced intestinal dysfunction. Histologically, the chemotherapy-induced injury of intestinal epithelium represents arrest of cell renewal, various degrees of villi atrophy, loss of absorbing surface, and increased mucosa permeability of cell tight junction. Indeed, we observed such destruction of intestinal mucosa in rats treated with 5-FU (**Figures 4** and **5**). In consistence with structural changes, serum levels of endotoxin, D-lactate and D-Amino-Acid Oxidase (DAO) were increased after 5-FU treatment (**Figure 3**). Traditional Chinese Medicines (TCMs) has attracted great attention as an alternative approach for the treatment of many human cancers [15-19]. Recently, TCMs were found to alleviate side effects of chemotherapy and improve intestinal mucosal permeability [20, 21]. In this study, Curcumin reversed 5-FU-induced destruction of intestinal mucosa structure and decreased serum levels of endotoxin, D-lactate and DAO. As a result, the animal behaviors were improved and weight-loss induced by 5-FU treatment was significantly rescued.

Interestingly, Curcumin can also effectively induce growth inhibition of human cancer cells probably by promoting the assembly of DNA-DNA topoisomerases (TOPOs) like many chemotherapeutic drugs [22]. Such an effect can be prevented by the antioxidant N-acetylcysteine (NAC), indicating that reactive oxygen species (ROS) may mediate the formation of these complexes [22]. In addition, Curcumin significantly sensitized human breast cancer cells (MCF-7 and MDA-MB-231) to MMC (Mitomycin)-induced cell apoptosis by activating caspases and modulating the expression of Bcl-2 and Bax [23]. Similarly, Curcumin synergistically enhance the in vitro and in vivo antitumor efficacy of other chemotherapeutic agents such as 5-FU, cisplatin and paclitaxel [24-26] or target therapy agents such as bortezomib and dasatinib [27, 28]. However, Curcumin was also found to antagonize the anti-cancer effect of etoposide [29]. This antagonism is related to the enhanced arrest of tumor cells in both S and G2/M phases that prevents the cells from entering M-phase with damaged DNA and consequent cell death by allowing efficient DNA damage repair. In addition, Curcumin also affected the expression of apoptosis-related genes such as Caspase-3, Bax and Bcl-2 (**Figure 6**). By regulating cellular apoptosis, proteins of the Bcl-2 family such as Bax and Bcl-2 are involved in 5-FU-induced apoptosis of intestinal epithelial cells. As shown in **Figure 6**, the expression of Bax and Caspase-3 were dramatically increased after 5-FU treatment that was consistent with the structural changes induced by 5-FU treatment. In contrast, Curcumin treatment significantly reduced the expression of pro-apoptotic Bax but stimulated the expression of anti-apoptotic Bcl-2.

In summary, Curcumin significantly reversed chemotherapy-induced weight-loss, increase of serum endotoxin, D-lactate and DAO and damage to intestinal mucosa. Curcumin also reduced the expression of pro-apoptotic Bax but stimulated anti-apoptotic Bcl-2 to attenuate 5-FU-induced apoptosis of intestinal epithelial cells. The clinical administration of Curcumin may improve chemotherapy-induced intestinal dysfunction, thus increasing the efficacy of chemotherapy.

Acknowledgements

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Disclosure of conflict of interest

All authors have no conflict of interest.

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