

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2017 July 14; 23(26): 4661-4846



### EDITORIAL

- 4661** Can a fibrotic liver afford epithelial-mesenchymal transition?

*Munker S, Wu YL, Ding HG, Liebe R, Weng HL*

- 4669** Impact of hepatitis C oral therapy in portal hypertension

*Libânio D, Marinho RT*

### REVIEW

- 4675** Present and future of metastatic colorectal cancer treatment: A review of new candidate targets

*Martini G, Troiani T, Cardone C, Vitiello P, Sforza V, Ciardiello D, Napolitano S, Della Corte CM, Morgillo F, Raucci A, Cuomo A, Selvaggi F, Ciardiello F, Martinelli E*

- 4689** Diarrhea after bariatric procedures: Diagnosis and therapy

*Borbély YM, Osterwalder A, Kröll D, Nett PC, Inglin RA*

### ORIGINAL ARTICLE

#### Basic Study

- 4701** Fibrinogen deficiency suppresses the development of early and delayed radiation enteropathy

*Wang J, Pathak R, Garg S, Hauer-Jensen M*

- 4712** *Helicobacter pylori* vacA genotype is a predominant determinant of immune response to *Helicobacter pylori* CagA

*Link A, Langner C, Schirrmeister W, Habendorf W, Weigt J, Venerito M, Tammer I, Schlüter D, Schlaermann P, Meyer TF, Wex T, Malfertheiner P*

- 4724** Jianpi Qingchang decoction regulates intestinal motility of dextran sulfate sodium-induced colitis through reducing autophagy of interstitial cells of Cajal

*Dai YC, Zheng L, Zhang YL, Chen X, Chen DL, Wang LJ, Tang ZP*

- 4735** *Lactobacillus acidophilus* alleviates pouchitis after ileal pouch-anal anastomosis in rats

*Xu YY, Zhang YY, He AQ, Li KY, Gao SY, Liu G*

- 4744** Effect of EPEC endotoxin and bifidobacteria on intestinal barrier function through modulation of toll-like receptor 2 and toll-like receptor 4 expression in intestinal epithelial cell-18

*Yang X, Gao XC, Liu J, Ren HY*

**Retrospective Cohort Study**

- 4752 Hospital costs, length of stay and prevalence of hip and knee arthroplasty in patients with inflammatory bowel disease

*Ehrenpreis ED, Zhou Y*

**Retrospective Study**

- 4759 Eight-week ledipasvir/sofosbuvir in non-cirrhotic, treatment-naïve hepatitis C genotype-1 patients with hepatitis C virus-RNA < 6 million IU/mL: Single center, real world effectiveness and safety

*Latt NL, Yanny BT, Gharibian D, Gevorkyan R, Sahota AK*

- 4767 Early radiological assessment of locally advanced pancreatic cancer treated with electrochemotherapy

*Granata V, Fusco R, Setola SV, Piccirillo M, Leongito M, Palaia R, Granata F, Lastoria S, Izzo F, Petrillo A*

- 4779 Effect of initial stent position on patency of transjugular intrahepatic portosystemic shunt

*Luo SH, Chu JG, Huang H, Yao KC*

**Observational Study**

- 4788 Endoscopy is of low yield in the identification of gastrointestinal neoplasia in patients with dermatomyositis: A cross-sectional study

*Kidambi TD, Schmajuk G, Gross AJ, Ostroff JW, Terdiman JP, Lee JK*

- 4796 Levels and activities of von Willebrand factor and metalloproteinase with thrombospondin type-1 motif, number 13 in inflammatory bowel diseases

*Cibor D, Owczarek D, Butenas S, Salapa K, Mach T, Undas A*

- 4806 Predictors of esophageal varices and first variceal bleeding in liver cirrhosis patients

*Kraja B, Mone I, Akshija I, Koçollari A, Prifti S, Burazeri G*

- 4815 Extreme liver resections with preservation of segment 4 only

*Balzan SMP, Gava VG, Magalhães MA, Dotto ML*

- 4823 Predictive factors for body weight loss and its impact on quality of life following gastrectomy

*Tanabe K, Takahashi M, Urushihara T, Nakamura Y, Yamada M, Lee SW, Tanaka S, Miki A, Ikeda M, Nakada K*

**Prospective Study**

- 4831 Divergent expression of bacterial wall sensing toll-like receptors 2 and 4 in colorectal cancer

*Paarnio K, Väyrynen S, Klintrup K, Ohtonen P, Mäkinen MJ, Mäkelä J, Karttunen TJ*

- 4839 Non-invasive assessment of liver fibrosis using two-dimensional shear wave elastography in patients with autoimmune liver diseases

*Zeng J, Huang ZP, Zheng J, Wu T, Zheng RQ*

## Contents

*World Journal of Gastroenterology*  
Volume 23 Number 26 July 14, 2017

### ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Seung-Wan Ryu, MD, PhD, Associate Professor, Division of Gastrointestinal Surgery, Department of Surgery, Keimyung university, Sch Med, Daegu 700-712, South Korea

### AIMS AND SCOPE

*World Journal of Gastroenterology* (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7<sup>th</sup>, 14<sup>th</sup>, 21<sup>st</sup>, and 28<sup>th</sup> each month. The *WJG* Editorial Board consists of 1375 experts in gastroenterology and hepatology from 68 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

### INDEXING/ABSTRACTING

*World Journal of Gastroenterology* (*WJG*) is now indexed in Current Contents<sup>®</sup>/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch<sup>®</sup>), Journal Citation Reports<sup>®</sup>, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2017 edition of Journal Citation Reports<sup>®</sup> cites the 2016 impact factor for *WJG* as 3.365 (5-year impact factor: 3.176), ranking *WJG* as 29<sup>th</sup> among 79 journals in gastroenterology and hepatology (quartile in category Q2).

### FLYLEAF

#### I-IX Editorial Board

### EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*  
Responsible Electronic Editor: *Dan Li*  
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Yuan Qi*  
Proofing Editorial Office Director: *Jin-Lei Wang*

NAME OF JOURNAL  
*World Journal of Gastroenterology*

ISSN  
ISSN 1007-9327 (print)  
ISSN 2219-2840 (online)

LAUNCH DATE  
October 1, 1995

FREQUENCY  
Weekly

EDITORS-IN-CHIEF  
**Damian Garcia-Olmo, MD, PhD, Doctor, Professor, Surgeon**, Department of Surgery, Universidad Autonoma de Madrid; Department of General Surgery, Fundacion Jimenez Diaz University Hospital, Madrid 28040, Spain

**Stephen C Strom, PhD, Professor**, Department of Laboratory Medicine, Division of Pathology, Karolinska Institutet, Stockholm 141-86, Sweden

**Andrzej S Tarnawski, MD, PhD, DSc (Med), Professor of Medicine, Chief Gastroenterology**, VA Long Beach Health Care System, University of California, Irvine, CA, 5901 E. Seventh Str., Long Beach,

CA 90822, United States

EDITORIAL BOARD MEMBERS  
All editorial board members resources online at <http://www.wjgnet.com/1007-9327/editorialboard.htm>

EDITORIAL OFFICE  
Jin-Lei Wang, Director  
Yuan Qi, Vice Director  
Ze-Mao Gong, Vice Director  
*World Journal of Gastroenterology*  
Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>

PUBLISHER  
Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>

<http://www.wjgnet.com>

PUBLICATION DATE  
July 14, 2017

COPYRIGHT  
© 2017 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT  
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS  
Full instructions are available online at <http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION  
<http://www.f6publishing.com>

## Basic Study

# ***Lactobacillus acidophilus* alleviates pouchitis after ileal pouch-anal anastomosis in rats**

Yan-Yan Xu, Ying-Ying Zhang, An-Qi He, Kai-Yu Li, Sen-Yang Gao, Gang Liu

Yan-Yan Xu, Ying-Ying Zhang, An-Qi He, Kai-Yu Li, Sen-Yang Gao, Gang Liu, Department of General Surgery, Tianjin Medical University General Hospital, Tianjin 300052, China

**Author contributions:** Liu G conceived and designed the study; Xu YY and Zhang YY collected the data; He AQ and Li KY contributed to data analysis; Xu YY, Gao SY and Zhang YY contributed to interpretation of the data; Liu G participated in streamlining the study protocol; Zhang YY, Xu YY and He AQ proofread the study protocol; Li KY and Gao SY supervised the data collection process; Li KY, Xu YY, Gao SY, Zhang YY and He AQ contributed to drafting the manuscript; all authors contributed to the revision of the manuscript and approved the final version.

**Supported by** Jie-Shou Li Gut Barrier Foundation, No. LJS\_201008.

**Institutional review board statement:** The study was reviewed and approved by Tianjin Medical University General Hospital Institutional Review Board, Tianjin 300052, China.

**Institutional animal care and use committee statement:** All procedures involving animals were reviewed and approved by the Institutional Animal Care and Use Committee of the Animal Ethical and Welfare Committee (IACUC protocol number: TMUaMEC2017001).

**Conflict-of-interest statement:** The authors have no financial or other conflicts of interest to disclose.

**Data sharing statement:** No additional data are available.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Correspondence to:** Gang Liu, MD, PhD, Department of General Surgery, Tianjin Medical University General Hospital, Tianjin 300052, China. [liugang@tjmugh.com.cn](mailto:liugang@tjmugh.com.cn)  
Telephone: +86-22-60362365  
Fax: +86-22-60362365

Received: February 6, 2017  
Peer-review started: February 8, 2017  
First decision: March 16, 2017  
Revised: March 30, 2017  
Accepted: May 4, 2017  
Article in press: May 4, 2017  
Published online: July 14, 2017

## Abstract

### AIM

To assess the therapeutic potential of *Lactobacillus acidophilus* (LA) for the treatment of pouchitis in a rat model.

### METHODS

Sprague Dawley rats underwent proctocolectomy and ileal pouch-anal anastomosis followed by administration of dextran sulfate sodium (DSS) to induce pouchitis. Rats with pouchitis were randomly divided into three groups: no intervention (NI), normal saline (NS, 3 mL/d normal saline for 7 d), and LA (3 mL/d LA at  $1 \times 10^{10}$  colony-forming units for 7 d). General body condition was recorded and pouch specimens were obtained for histological examination. mRNA expression levels of interleukin (IL)-1 $\beta$ , IL-6, IL-10, and tumor necrosis factor- $\alpha$  were determined by RT-PCR. Zonula occludens protein 1 (ZO-1) levels were measured by immunohistochemistry.

### RESULTS

LA reduced weight loss associated with pouchitis ( $P < 0.05$ ) and improved the symptoms of pouchitis in rats. Compared with the NI and NS groups, rats in the LA



group showed earlier disappearance of hematochezia ( $6.17 \pm 0.75$ ,  $6.50 \pm 0.55$ ,  $3.17 \pm 0.75$ ,  $P < 0.05$ ) and higher fecal scores ( $2.67 \pm 0.48$ ,  $2.50 \pm 0.51$ ,  $4.42 \pm 0.50$ , respectively,  $P < 0.05$ ). Histological scores were also lower in the LA group compared with the other two groups ( $7.17 \pm 0.98$ ,  $8.00 \pm 0.89$ ,  $4.00 \pm 0.89$ , respectively,  $P < 0.05$ ). mRNA expression levels of IL-1 $\beta$ , IL-6, and tumor necrosis factor- $\alpha$  were significantly reduced, while IL-10 mRNA levels were significantly increased in the LA group ( $P < 0.05$ , respectively). ZO-1 protein levels were also significantly increased after administration of LA ( $P < 0.05$ ).

## CONCLUSION

LA alleviates pouchitis induced by DSS after ileal pouch-anal anastomosis by decreasing pro-inflammatory factors and increasing anti-inflammatory factors, and restoring ZO-1 expression in the mucosa.

**Key words:** *Lactobacillus acidophilus*; Pouchitis; Ileal pouch-anal anastomosis; Dextran sulfate sodium; Rats

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** This study aimed to assess the therapeutic potential of *Lactobacillus acidophilus* (LA) for the treatment of pouchitis in a rat model. Rats with pouchitis were randomly divided into three groups: no intervention, normal saline (NS, 3 mL/d normal saline for 7 d), and LA (3 mL/d LA at  $1 \times 10^{10}$  colony-forming units for 7 d). General body condition was recorded and pouch specimens were obtained for histological examination. mRNA expression levels of interleukin (IL)-1 $\beta$ , IL-6, IL-10, and tumor necrosis factor- $\alpha$  were determined by RT-PCR. Zonula occludens protein 1 levels were measured by immunohistochemistry.

Xu YY, Zhang YY, He AQ, Li KY, Gao SY, Liu G. *Lactobacillus acidophilus* alleviates pouchitis after ileal pouch-anal anastomosis in rats. *World J Gastroenterol* 2017; 23(26): 4735-4743 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i26/4735.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i26.4735>

## INTRODUCTION

Ulcerative colitis (UC) is defined as a chronic nonspecific inflammatory disorder with recurrent symptoms, involving the mucosa and submucosa of the colon and rectum<sup>[1]</sup>. Ileal pouch-anal anastomosis (IPAA) is an ideal surgical treatment for UC, allowing complete removal of the colorectal lesion while retaining the anus and avoiding the need for a permanent ileostomy. Ileal pouchitis is a common complication after IPAA in patients with UC, and occurs in approximately 50% of patients<sup>[2]</sup>. However, the pathogenesis of pouchitis is unclear and basic studies regarding this complication are lacking.

*Lactobacillus acidophilus* (LA) is a gram-positive bacterium that can form a protein crystal layer on the surface of intestinal cells<sup>[3]</sup>, thus conferring a protective effect on the intestinal barrier. The intestinal microbiota are considered to play a vital role in the development of UC<sup>[4]</sup> and pouchitis. Gionchetti *et al*<sup>[5]</sup> demonstrated the efficacy of probiotics such as VSL#3 for the prophylaxis and treatment of pouchitis, and our results are consistent with the results of this study. However, although various studies have shown beneficial effects of probiotics on the prevention and treatment of pouchitis, the specific mechanism remains unclear. Furthermore, the ability of specific bacteria and their combination to improve pouch inflammation is unknown<sup>[6]</sup>.

Interleukin (IL)-1 $\beta$  is a multi-protein complex, which can play an important role in the maintenance of intestinal immune balance through the identification of bacteria and injury-related molecules<sup>[7]</sup>. IL-6 is an important inflammatory factor secreted by endothelial cells, macrophages, and mast cells, and participates in the activation of lymphocytes<sup>[8]</sup>. Tumor necrosis factor (TNF)- $\alpha$  plays a key role in intestinal inflammation, involving multiple immune responses, affecting the expression of endothelial cell adhesion molecules and maintaining intestinal permeability<sup>[9]</sup>. IL-10 is a regulatory cytokine secreted by mononuclear macrophages and plays an anti-inflammatory role<sup>[10]</sup>. Intestinal inflammation is often accompanied by abnormalities in inflammatory factors such as IL-1 $\beta$ , IL-6, TNF- $\alpha$  and IL-10, which may reflect the severity of inflammation in pouchitis<sup>[11]</sup>. Furthermore, damage to the intestinal mucosal barrier is often accompanied by destruction of tight junction proteins, especially the loss of zonula occludens protein-1 (ZO-1), leading to increased intestinal permeability and further increasing the intestinal inflammatory response<sup>[12]</sup>. Rats subjected to IPAA provide an effective model for the study of pouchitis<sup>[13]</sup>. Shebani *et al*<sup>[14]</sup> established a rat model of dextran sulfate sodium (DSS)-induced pouchitis suitable for further studies of the pathogenesis of the disease.

We investigated the therapeutic effect of probiotic LA in a DSS rat model of ileal pouchitis, including determination of the expression of inflammatory markers (IL-1 $\beta$ , IL-6, TNF- $\alpha$  and IL-10) and ZO-1 protein in the intestinal mucosa by immunohistochemistry.

## MATERIALS AND METHODS

### Animals

Male Sprague Dawley rats ( $n = 18$ ) weighing 360-380 g (purchased from the Laboratory Animal Center of the Military Medical Science Academy of the Chinese People's Liberation Army) were housed individually in a specific pathogen-free animal laboratory at a temperature of 25 °C with a 12 h light/dark cycle, and provided with standard rat chow and running water *ad libitum*. Animal care and experiments were conducted

**Table 1** Primers used for reverse transcription-polymerase chain reaction

	Oligonucleotide sequence (5'-3')	Product length (bp)
IL-1 $\beta$		190
sense	5'-AATGCCTCGTGCTGTGACC-3'	
antisense	5'-GTGGGTGTGCCGTCCTTCATCA-3'	
IL-6		111
sense	5'-GACTTCCAGCCAGTTCCTTCT-3'	
antisense	5'-TGGTCTGTTGTGGGTGGTATCC-3'	
IL-10		196
sense	5'-GGGTGCCAAGCCTTGTGAGAA-3'	
antisense	5'-CTTCACCTGCTCCACTGCCTTG-3'	
TNF- $\alpha$		113
sense	5'-GGGCTCCCTCTCATCAGTTCCA-3'	
antisense	5'-TGCTCCTCCGTTGGTGGTT-3'	
R-GAPDH		122
sense	5'-TACCCACGGCAAGTTCAACG-3'	
antisense	5'-CACCAGCATACCCCCATTG-3'	

IL: Interleukin; TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ .

according to the international guidelines on animal research and ethics.

### Ileal pouchitis model

IPAA was performed by microsurgery and pouchitis was induced by administration of 4% DSS for 4 successive days after postoperative day 31. Rats with pouchitis were divided randomly into three groups: no intervention (NI) group, normal saline (NS) group, and LA group ( $n = 6$  per group). Rats in the NS group received 3 mL/d normal saline by lavage, and rats in the LA group received 3 mL/d LA at a concentration of  $1 \times 10^{10}$  colony-forming units for 7 d by lavage.

### General body condition and sample collection

Body weight changes, hematochezia, and fecal scores were observed and recorded in all rats before sacrifice under anesthesia on day 7 after LA or normal saline intervention. Fecal scores were evaluated on a 5-point scale according to the method described by Drzymala-Czyż *et al.*<sup>[15]</sup>: (1) lack of stool; (2) diarrhea; (3) blob of stool; (4) textured stool; and (5) normal stool. The ileal pouch was harvested after sacrifice and washed with normal saline. Half of each sample was fixed in 10% neutral formalin solution for histological examination and immunohistochemistry, and the remaining portion was immediately frozen in liquid nitrogen and stored at  $-80^{\circ}\text{C}$  for RT-PCR analysis.

### Histological assessment of pouchitis tissue

Tissues were paraffin-embedded, stained with hematoxylin and eosin, and examined under a microscope. Pouch specimens were assessed according to the criteria described by Atila *et al.*<sup>[16]</sup>. Erosion was evaluated as: 0, negative; 1, focal erosion; 2, erosion in many regions; or 3, extensive erosion. Ulceration was evaluated as: 0, none; 1, focal ulceration of the mucosa in half the superficial regions; 2, total mucosal

ulceration at multiple foci; or 3, extensive mucosal ulceration extending to the muscularis mucosa or beyond. Intra-epithelial inflammation was evaluated by counting the number of lymphocytes in 100 epithelial cells at the tips of the villi. Villous atrophy was evaluated as: 0, none; 1, mild; 2, moderate; or 3, severe with villous flattening. Edema at the lamina propria was evaluated as: 0, none or 1, positive. Abscess formation and submucosal inflammation were also evaluated.

### RT-PCR detection of IL-1 $\beta$ , IL-6, IL-10 and TNF- $\alpha$ mRNA

IL-1 $\beta$ , IL-6, IL-10 and TNF- $\alpha$  mRNA were detected using a RT-PCR kit (MJ-RESEARCH, United States) according to the manufacturer's instructions. Total RNA was extracted from pouch tissues using an animal tissue total RNA Extraction Kit (Tiangen, Beijing, China). The primer pairs are shown in Table 1.

### Immunohistochemistry

Samples were subjected to immunohistochemistry to assess the expression of ZO-1 protein, using rabbit anti-ZO-1 (PB0072) (Boster, WuHan, China). Immunohistochemical images were analyzed using Image-Pro Plus6.0 software to assess the optical density.

### Statistical analysis

All statistical analyses were carried out using SPSS 19.0. The data were expressed as the mean  $\pm$  SD. Data analysis was performed using independent-samples *t*-tests or one-way ANOVA, and comparisons of two among the three groups were made using Students-Newman-Keuls tests. A difference of  $P < 0.05$  was considered statistically significant.

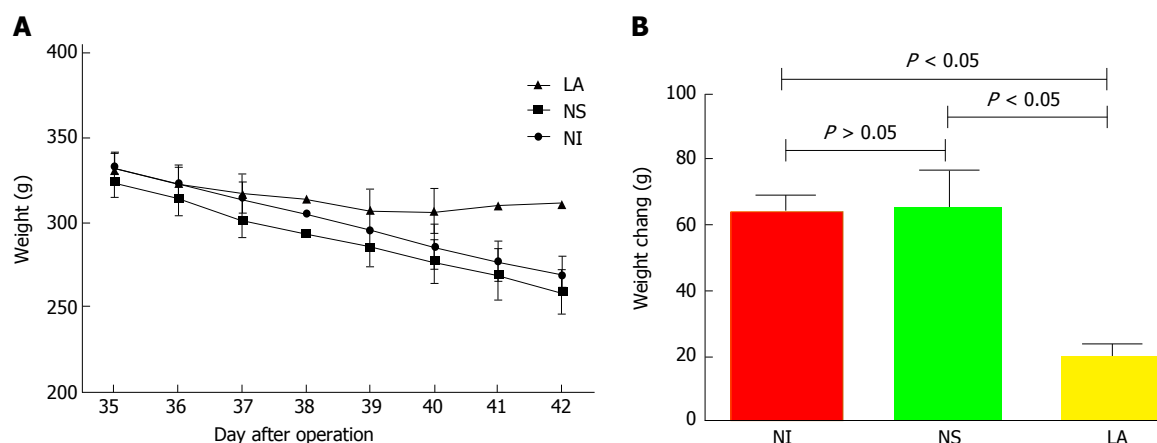
## RESULTS

### Changes in physiological condition

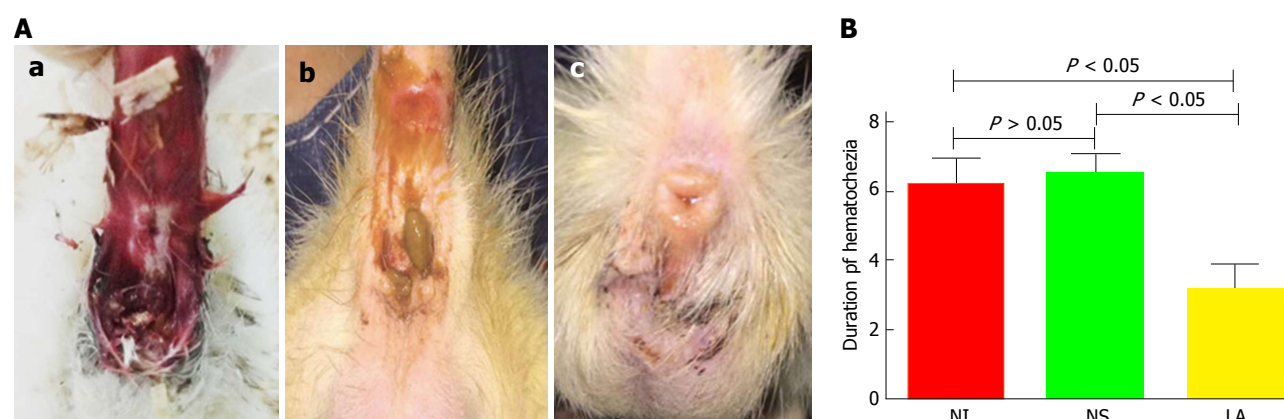
Rat body weight decreased linearly after the generation of pouchitis ( $72.92 \pm 6.60$ ). Following intervention for 7 d, body weight in the NI ( $63.50 \pm 5.99$ ) and NS groups ( $64.67 \pm 11.93$ ) continued to decline (Figure 1A), with no significant difference between the two groups ( $P > 0.05$ ). However, the weight of rats in the LA group which initially decreased started to increase again on day 4 of lavage with LA ( $20.17 \pm 3.25$ ). The difference in body weights among the three groups was significant ( $F = 61.34$ ,  $P < 0.05$ ) (Figure 1B).

Bloody stools were observed in all groups at the end of the DSS intervention. Hematochezia disappeared in the LA group at  $3.17 \text{ d} \pm 0.75 \text{ d}$ , and in the NS and NI groups at  $6.50 \text{ d} \pm 0.55 \text{ d}$  and  $6.17 \text{ d} \pm 0.75 \text{ d}$ , respectively. The recovery time in the LA group was significantly shorter than in the NS and NI groups ( $F = 108.70$ ,  $P < 0.05$ ) (Figure 2).

Stools in the NI and NS groups had a similar, loose-paste appearance (Figure 3A) and there was no significant difference in fecal scores between the



**Figure 1** Changes in rat body weight during the experiment. A: Body weight changes in rats following pouchitis. Weight in the NI ( $63.50 \pm 5.99$ ) and NS groups ( $64.67 \pm 11.93$ ) continued to decline, while weight in the LA group initially decreased and then increased on day 4 of LA lavage ( $20.17 \pm 3.25$ ); B: The differences in body weight among the three groups were statistically significant ( $F = 61.34$ ,  $P < 0.05$ ), but there was no significant difference between the NI and NS groups ( $P > 0.05$ ). NI: No Intervention group; NS: Normal Saline group; LA: *Lactobacillus acidophilus* group.



**Figure 2** Hematochezia in rats. A: Anal condition of rats in each group at 4 d post-intervention. The NI (a) and NS groups (b) still had hematochezia, but this had disappeared in the LA group (c); B: Recovery was significantly faster in the LA group compared with the NS and NI groups ( $F = 108.70$ ,  $P < 0.05$ ). NI: No Intervention group; NS: Normal Saline group; LA: *Lactobacillus acidophilus* group.

NI ( $2.67 \pm 0.48$ ) and NS groups ( $2.50 \pm 0.51$ ) ( $t = 1.16$ ,  $P > 0.05$ ). However, feces in the LA group ( $4.42 \pm 0.50$ ) were more normal, and the fecal score was significantly higher than in the NI ( $t = 12.30$ ,  $P < 0.05$ ) and NS groups ( $t = 13.09$ ,  $P < 0.05$ ) (Figure 3B).

### Histopathological changes and pouch scores

In terms of gross morphology, mucosal surface congestion and edema, toughness, visible multiple ulcers, and scattered bleeding were observed in the NI and NS groups, but mucosal congestion and edema were less evident in the LA group (Figure 4A).

On microscopic examination, the structure of the mucosal villi in the pouch tissue was irregular and disordered, the passivation of the villi, with extensive inflammatory cell infiltration in the central matrix of the villi in the NI and NS groups, while less severe lesions were observed in the LA group (Figure 4B). There was no significant difference in histological scores between the NI ( $7.17 \pm 0.98$ ) and NS groups ( $8.00 \pm 0.89$ ) ( $t = 1.536$ ,  $P > 0.05$ ), but the histological score

was significantly lower in the LA group ( $4.00 \pm 0.89$ ) compared with the other two groups ( $F = 5.84$ ,  $P < 0.05$ ) (Figure 4C).

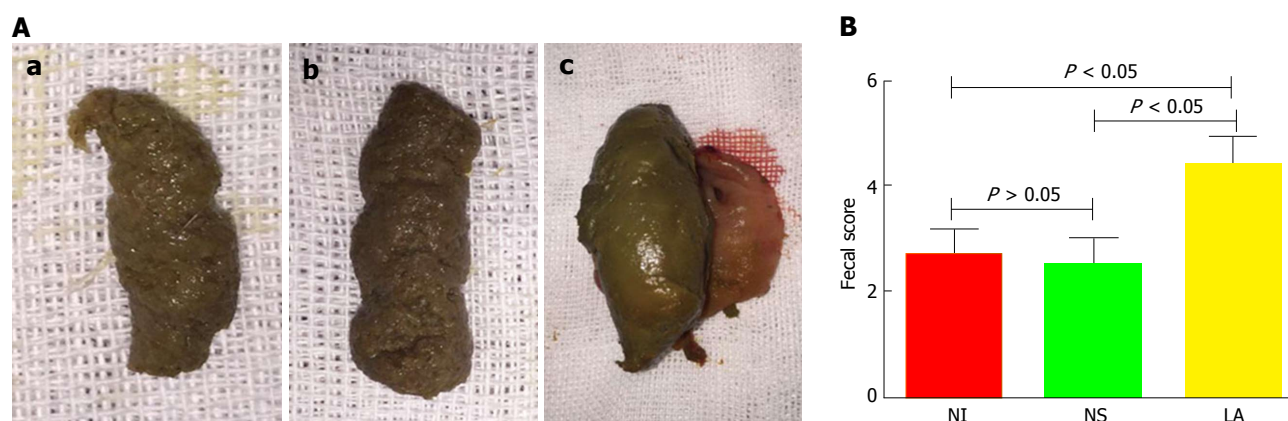
### Expression of IL-1 $\beta$ , IL-6, IL-10, and TNF- $\alpha$ mRNA

mRNA levels of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  in the LA group were significantly lower than in the NS and NI groups ( $F = 373.60$ ,  $P < 0.05$ ;  $F = 285.50$ ,  $P < 0.05$ ;  $F = 132.90$ ,  $P < 0.05$ , respectively). In contrast, IL-10 mRNA levels were significantly higher in the LA group compared with the other two groups ( $F = 61.05$ ,  $P < 0.05$ ). There was no significant difference in expression levels of inflammatory factors between the NS and NI groups ( $P > 0.05$ ) (Figure 5).

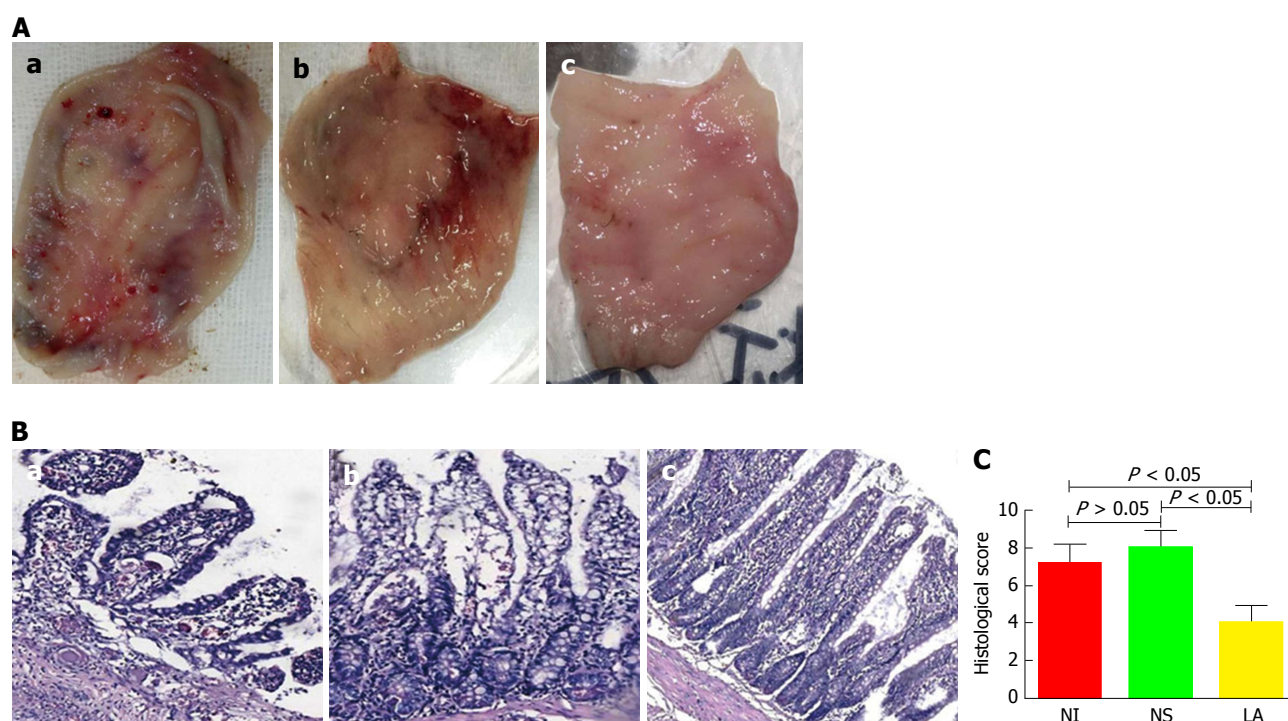
### Expression levels of ZO-1 protein

ZO-1 is a tight junction protein, indicated by yellow staining in the cell membrane (Figure 6A). ZO-1 protein expression levels were significantly lower in the NI ( $0.27 \pm 0.03$ ) and NS groups ( $0.22 \pm 0.08$ ) compared with the LA group ( $0.35 \pm 0.02$ ) ( $F = 8.23$ ,  $P < 0.05$ ).





**Figure 3 Feces of rats.** A: Stools appeared as loose paste in the NI (a) and NS (b) groups, but were more normal in the LA group (c); B: The fecal score was significantly higher in the LA group compared with the NI ( $t = 12.30$ ,  $P < 0.05$ ) and NS groups ( $t = 13.09$ ,  $P < 0.05$ ). NI: No Intervention group; NS: Normal Saline group; LA: *Lactobacillus acidophilus* group.



**Figure 4 Gross and microscopic histological observations.** A: Mucosal surface congestion and edema, toughness, visible multiple ulcers, and scattered bleeding were evident in the NI (a) and NS (b) groups, but mucosal congestion and edema had disappeared in the LA (c) group; B: Microscopic examination of the pouch revealed irregular and disordered mucosal villi, passivation of the villi, and extensive inflammatory cell infiltration in the central matrix of the villi in the NI (a) and NS (b) groups, but less severe lesions in the LA (c) group; C: There was no significant difference in histological scores between the NI ( $7.17 \pm 0.98$ ) and NS groups ( $8.00 \pm 0.89$ ) ( $t = 1.536$ ,  $P > 0.05$ ), but the histological score was significantly lower in the LA group ( $4.00 \pm 0.89$ ) than in the other two groups ( $F = 5.84$ ,  $P < 0.05$ ). NI: No Intervention group; NS: Normal Saline group; LA: *Lactobacillus acidophilus* group.

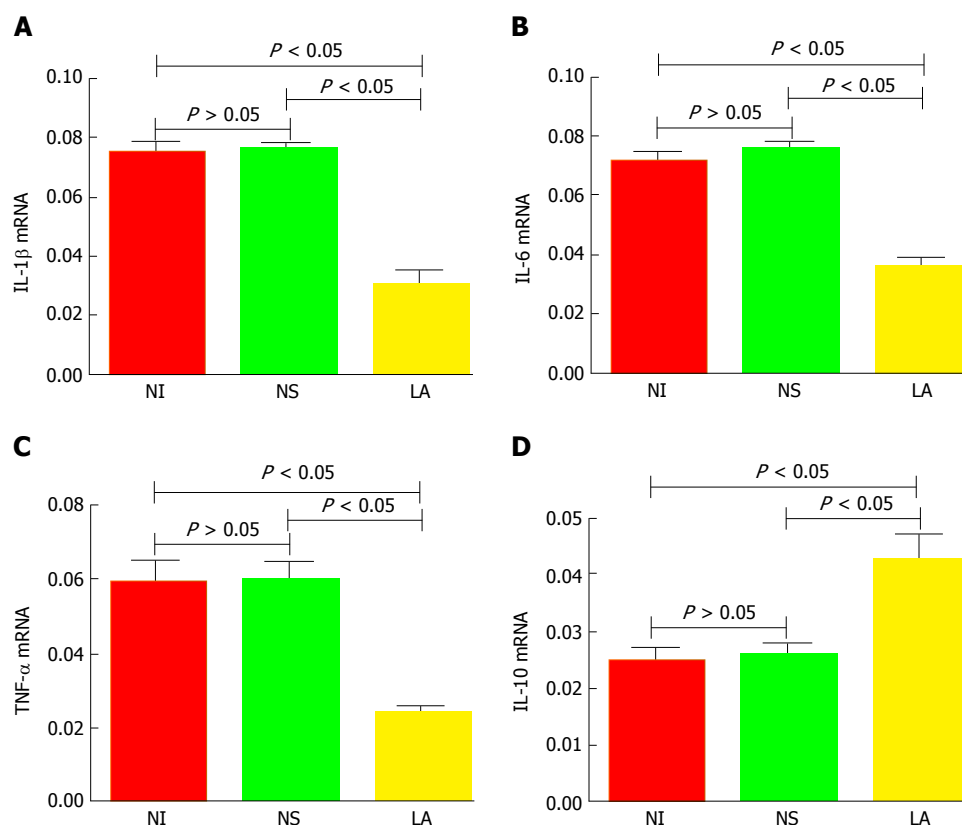
(Figure 6B).

## DISCUSSION

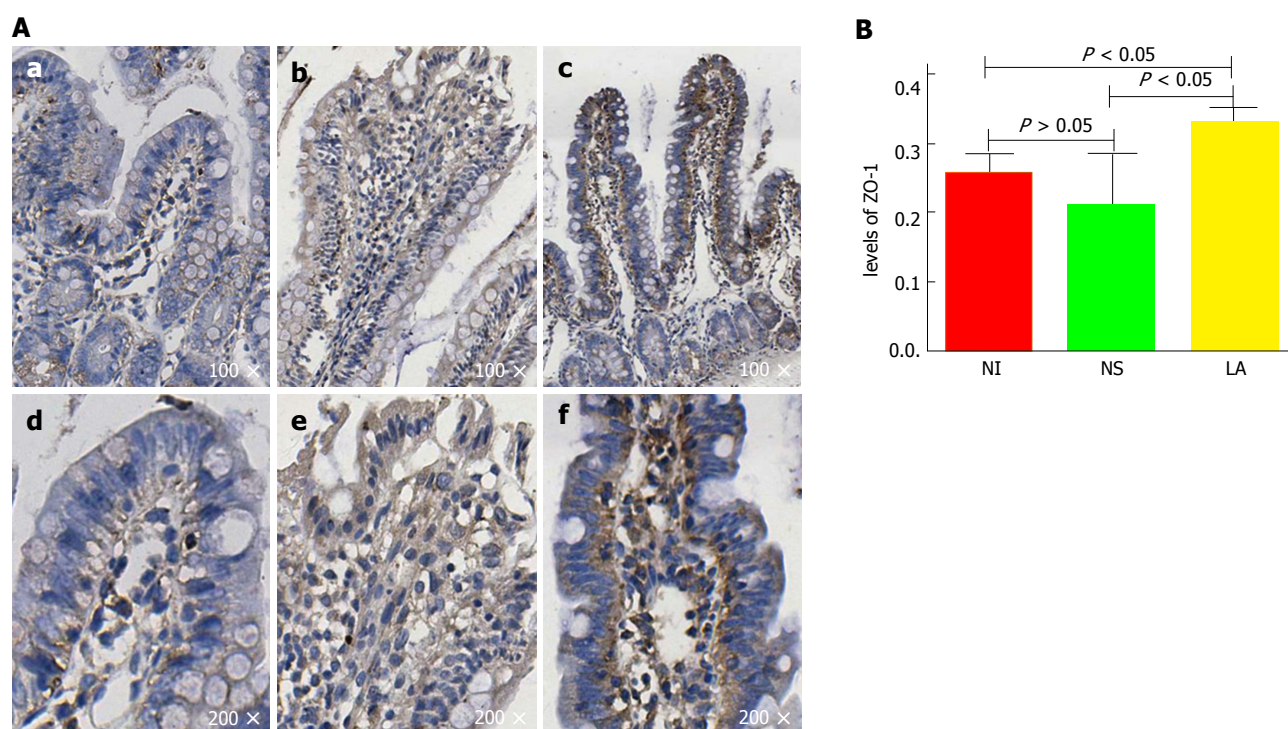
The intestinal microflora is generally thought to be involved in the pathogenesis of inflammatory bowel disease (IBD)<sup>[17]</sup>. The numbers of intestinal *Bifidobacterium* and *Lactobacillus* were decreased and *Clostridium perfringens* was significantly increased in patients with pouchitis<sup>[18]</sup>. LA is a component of VSL#3, and VSL#3,

which is beneficial for maintaining remission in patients with pouchitis<sup>[19,20]</sup>. Probiotics containing LA can reduce expression of the inflammatory cytokine IL-1 $\beta$  and inhibit inflammatory damage caused by infiltration of polymorphonuclear cells in the tissues. Lammers *et al*<sup>[11]</sup> suggested that probiotics could be used to prevent and treat pouchitis, and LA has also shown immunomodulatory effects in *in vitro* experiments<sup>[21-24]</sup>.

NaCl absorption involves coupling of the Cl<sup>-</sup>/HCO<sup>3-</sup> exchanger(s) primarily with the Na<sup>+</sup>/H<sup>+</sup> exchanger 3 at



**Figure 5 mRNA expression levels.** mRNA levels of IL-1 $\beta$  (A), IL-6 (B), and TNF- $\alpha$  (C) were significantly lower in the LA group compared with the NS and NI groups ( $F = 373.60$ ,  $P < 0.05$ ;  $F = 285.50$ ,  $P < 0.05$ ;  $F = 132.90$ ,  $P < 0.05$ , respectively), while IL-10 (D) levels were significantly higher ( $F = 61.05$ ,  $P < 0.05$ ). IL: Interleukin; TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ ; NI: No Intervention group; NS: Normal Saline group; LA: *Lactobacillus acidophilus* group.



**Figure 6 Zonula occludens protein 1 protein expression levels.** A: ZO-1 protein expression levels in the NI (a, d) and NS groups (b, e) were significantly lower than in the LA group (c, f); B: The differences between the three groups were statistically significant ( $F = 8.23$ ,  $P < 0.05$ ). ZO-1: Zonula occludens protein 1; NI: No Intervention group; NS: Normal Saline group; LA: *Lactobacillus acidophilus* group.

the apical membrane of intestinal epithelia. Disturbances to this process occur in diarrheal diseases<sup>[25]</sup>, and may also be involved in the formation of mucus stools in pouchitis. LA-conditioned medium stimulated intestinal cells to absorb NaCl by different mechanisms in *in vitro* experiments, and this mechanism may be an important factor in the improvement and treatment of IBD-associated diarrhea symptoms<sup>[26,27]</sup>. Borthakur *et al.*<sup>[26]</sup> found that LA increased the exchange effect by increasing cell surface phosphoinositide 3-kinase dependent Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> channels. Singh *et al.*<sup>[27]</sup> showed that LA could promote the expression of Na<sup>+</sup>/H<sup>+</sup> exchanger 3 (SLC9A3), which is widespread in epithelial cells of the digestive tract, resulting in improved intestinal absorption of electrolytes and an antidiarrheal effect. Chen *et al.*<sup>[28]</sup> showed that LA was able to prevent bacterial colitis and activate the immune response with a protective effect on the intestinal mucosa.

Changes in intestinal inflammation are often accompanied by abnormalities in a range of inflammatory cytokines, including IL-1 $\beta$ , IL-6, TNF- $\alpha$  and IL-10, and the level of inflammation can be determined by detecting changes in these inflammatory factors in the pouch mucosa<sup>[11]</sup>. The results showed that the expression levels of IL-1 $\beta$ , IL-6 and TNF- $\alpha$  were significantly higher in patients with pouchitis than in those with active UC and non-pouchitis. Intestinal tract damage can lead to activation of the inflammatory response resulting in activation of caspase-1 and release of IL-1 $\beta$ <sup>[29]</sup>. Our study found that the expression of IL-1 $\beta$  in pouch tissues was significantly increased after pouchitis was induced by DSS, and compared with the control group, LA can significantly reduce the expression of IL-1 $\beta$ .

IL-6 expression levels were significantly increased in intestinal tissues of rats with inflammation. The interaction of antigen presenting cells with bacteria in IBD patients was shown to result in abnormal activation of CD4<sup>+</sup> T cells, causing continuous release of pro-inflammatory cytokines and increased levels of IL-6 and TNF- $\alpha$ <sup>[30]</sup>. Our results showed that the expression levels of IL-6 and TNF- $\alpha$  in the mucosa of DSS-induced pouchitis were significantly higher than those in the control group, while the expression was decreased following LA gavage and the pathological score of the pouch was significantly decreased. Sang *et al.*<sup>[31]</sup> treated rats with colitis using VSL#3 and showed that probiotics could significantly reduce IL-6 expression in intestinal tissues. Chen *et al.*<sup>[32]</sup> also found that LA could significantly inhibit the expression of TNF- $\alpha$  in the intestinal mucosa in a rat colitis model.

IL-10 has previously been shown to play an anti-inflammatory role in pouchitis<sup>[33]</sup>, and LA significantly increased IL-10 expression in human peripheral blood cells<sup>[34]</sup>. The results of the current study showed that DSS caused an intestinal inflammatory response in rats, associated with significantly increased levels of

IL-1 $\beta$ , IL-6, and TNF- $\alpha$ , and significantly decreased levels of IL-10. This is consistent with the results of Chen *et al.*<sup>[35]</sup>, who used probiotics in a DSS-induced pouchitis model in rats. In addition, IL-6 can increase the amount of myeloperoxidase (MPO) by activating neutrophils, the increase in MPO protein not only reflects the degree of inflammation, but can produce a large number of oxygen free radicals in the intestinal barrier and further aggravate intestinal inflammation.

ZO-1 is a member of the membrane-associated guanylate kinases family<sup>[36]</sup>. Shen *et al.*<sup>[37]</sup> showed that abnormal tight junctions resulted in increased permeability of the intestinal barrier, often accompanied by decreased expression of ZO-1 protein. Changes in the intestinal barrier caused by reduced ZO-1 expression in the intestinal tract will further promote the development of intestinal inflammation<sup>[12]</sup>. ZO-1 decreased following DSS administration in a rat colitis model, and the severity of colitis increased with time<sup>[12]</sup>. Our results also showed that ZO-1 expression levels were significantly higher in the LA group compared with the NI and NS groups, accompanied by decreased expression of inflammatory factors and improved pathological changes.

In summary, DSS-induced destruction of the intestinal barrier in the pouch manifested as increased levels of pro-inflammatory IL-1 $\beta$ , IL-6 and TNF- $\alpha$ , and decreased levels of anti-inflammatory IL-10, together with decreased expression of the intestinal barrier tight junction protein ZO-1. These factors reflect a complex network with the potential to aggravate mucosal inflammation in the pouch. LA may reduce the expression of pro-inflammatory factors and increase anti-inflammatory factors through a variety of mechanisms, increase expression of the tight junction protein ZO-1 in the intestinal mucosa thus promoting recovery of intestinal mucosal barrier function, and block interactions among various pro-inflammatory factors. Further studies are needed to clarify the potential role of LA in the prevention and treatment of pouchitis.

## COMMENTS

### Background

Ileal pouchitis is a common complication after ileal pouch-anal anastomosis (IPAA) in patients with ulcerative colitis (UC), and occurs in approximately 50% of patients. However, the pathogenesis of pouchitis is unclear and basic studies regarding this complication are lacking. *Lactobacillus acidophilus* (LA) confers a protective effect on the intestinal barrier, but the therapeutic potential of LA on pouchitis is uncertain.

### Research frontiers

Gastrointestinal microbiota in the field of inflammatory bowel disease (IBD) and pouchitis is a hot research topic.

### Innovations and breakthroughs

Flora imbalance is involved in the pathogenesis of IBD, and has a similar role in the genesis and development of pouchitis. The authors confirmed that LA can be effective in the treatment of pouchitis, which provides a new treatment option



for pouchitis.

## Applications

This study provides a new treatment option for pouchitis. The successful application of LA in the treatment of pouchitis in rat models has indicated that further research on microbial treatment in humans should be carried out.

## Terminology

Pouchitis: An intestinal pouch complication of the IPAA procedure in patients with UC. Symptoms of pouchitis include diarrhea, hematochezia, increased stool frequency and abdominal cramps. LA: LA is a gram-positive bacterium that can form a protein crystal layer on the surface of intestinal cells, thus conferring a protective effect on the intestinal barrier and plays a vital role in the development of UC and pouchitis.

## Peer-review

This manuscript is an interesting and well written paper regarding possible facilitatory effects of LA pouchitis in a rat model of IPAA.

## REFERENCES

- 1 **Ordás I**, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. *Lancet* 2012; **380**: 1606-1619 [PMID: 22914296 DOI: 10.1016/S0140-6736(12)60150-0]
- 2 **Pardi DS**, D'Haens G, Shen B, Campbell S, Gionchetti P. Clinical guidelines for the management of pouchitis. *Inflamm Bowel Dis* 2009; **15**: 1424-1431 [PMID: 19685489 DOI: 10.1002/ibd.21039]
- 3 **Hynönen U**, Palva A. Lactobacillus surface layer proteins: structure, function and applications. *Appl Microbiol Biotechnol* 2013; **97**: 5225-5243 [PMID: 23677442 DOI: 10.1007/s00253-013-4962-2]
- 4 **Martinez C**, Antolin M, Santos J, Torrejon A, Casellas F, Borrue N, Guarner F, Malagelada JR. Unstable composition of the fecal microbiota in ulcerative colitis during clinical remission. *Am J Gastroenterol* 2008; **103**: 643-648 [PMID: 18341488 DOI: 10.1111/j.1572-0241.2007.01592.x]
- 5 **Gionchetti P**, Rizzello F, Venturi A, Brigidi P, Matteuzzi D, Bazzocchi G, Poggioli G, Miglioli M, Campieri M. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; **119**: 305-309 [PMID: 10930365]
- 6 **Batista D**, Raffals L. Role of intestinal bacteria in the pathogenesis of pouchitis. *Inflamm Bowel Dis* 2014; **20**: 1481-1486 [PMID: 25046009 DOI: 10.1097/MIB.000000000000055]
- 7 **Strowig T**, Henao-Mejia J, Elinav E, Flavell R. Inflammasomes in health and disease. *Nature* 2012; **481**: 278-286 [PMID: 22258606 DOI: 10.1038/nature10759]
- 8 **Ammori JB**, Zhang WZ, Li JY, Chai BX, Mulholland MW. Effects of ghrelin on neuronal survival in cells derived from dorsal motor nucleus of the vagus. *Surgery* 2008; **144**: 159-167 [PMID: 18656621 DOI: 10.1016/j.surg.2008.03.008]
- 9 **Apostolaki M**, Armaka M, Victoratos P, Kollias G. Cellular mechanisms of TNF function in models of inflammation and autoimmunity. *Curr Dir Autoimmun* 2010; **11**: 1-26 [PMID: 20173385 DOI: 10.1159/000289195]
- 10 **Hessle C**, Andersson B, Wold AE. Gram-positive bacteria are potent inducers of monocytic interleukin-12 (IL-12) while gram-negative bacteria preferentially stimulate IL-10 production. *Infect Immun* 2000; **68**: 3581-3586 [PMID: 10816515]
- 11 **Lammers KM**, Vergopoulos A, Babel N, Gionchetti P, Rizzello F, Morselli C, Caramelli E, Fiorentino M, d'Errico A, Volk HD, Campieri M. Probiotic therapy in the prevention of pouchitis onset: decreased interleukin-1beta, interleukin-8, and interferon-gamma gene expression. *Inflamm Bowel Dis* 2005; **11**: 447-454 [PMID: 15867584]
- 12 **Poritz LS**, Garver KI, Green C, Fitzpatrick L, Ruggiero F, Koltun WA. Loss of the tight junction protein ZO-1 in dextran sulfate sodium induced colitis. *J Surg Res* 2007; **140**: 12-19 [PMID: 17418867 DOI: 10.1016/j.jss.2006.07.050]
- 13 **Lichtman SN**, Wang J, Hummel B, Lacey S, Sartor RB. A rat model of ileal pouch-rectal anastomosis. *Inflamm Bowel Dis* 1998; **4**: 187-195 [PMID: 9741020]
- 14 **Shebani KO**, Stocchi AF, Fruin B, McClung JP, Gee D, Beer ER, LaMorte WW, Becker JM. Pouchitis in a rat model of ileal J pouch-anal anastomosis. *Inflamm Bowel Dis* 2002; **8**: 23-34 [PMID: 11837935]
- 15 **Drzymala-Czyż S**, Banasiewicz T, Tubacka M, Tarasiuk-Rusek A, Majewski P, Drews M, Walkowiak J. Discrepancy between clinical and histological effects of DHA supplementation in a rat model of pouchitis. *Folia Histochem Cytobiol* 2012; **50**: 125-129 [PMID: 22532147 DOI: 10.2478/18707]
- 16 **Atila K**, Terzi C, Canda AE, Akhisaroglu ST, Avci HS, Sarioglu S, Oktay G, Gulay Z. Partially hydrolyzed guar gum attenuates the severity of pouchitis in a rat model of ileal J pouch-anal anastomosis. *Dig Dis Sci* 2009; **54**: 522-529 [PMID: 18594969 DOI: 10.1007/s10620-008-0377-9]
- 17 **Frank DN**, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc Natl Acad Sci USA* 2007; **104**: 13780-13785 [PMID: 17699621 DOI: 10.1073/pnas.0706625104]
- 18 **Iwaya A**, Iiai T, Okamoto H, Ajioka Y, Yamamoto T, Asahara T, Nomoto K, Hatakeyama K. Change in the bacterial flora of pouchitis. *Hepatogastroenterology* 2006; **53**: 55-59 [PMID: 16506376]
- 19 **Shen J**, Zuo ZX, Mao AP. Effect of probiotics on inducing remission and maintaining therapy in ulcerative colitis, Crohn's disease, and pouchitis: meta-analysis of randomized controlled trials. *Inflamm Bowel Dis* 2014; **20**: 21-35 [PMID: 24280877 DOI: 10.1097/01.MIB.0000437495.30052.be]
- 20 **Gionchetti P**, Calabrese C, Lauri A, Rizzello F. The therapeutic potential of antibiotics and probiotics in the treatment of pouchitis. *Expert Rev Gastroenterol Hepatol* 2015; **9**: 1175-1181 [PMID: 26202437 DOI: 10.1586/17474124.2015.1072046]
- 21 **Sahay B**, Ge Y, Colliou N, Zadeh M, Weiner C, Mila A, Owen JL, Mohamadzadeh M. Advancing the use of Lactobacillus acidophilus surface layer protein A for the treatment of intestinal disorders in humans. *Gut Microbes* 2015; **6**: 392-397 [PMID: 26647142 DOI: 10.1080/19490976.2015.1107697]
- 22 **Li L**, Jiang YJ, Yang XY, Liu Y, Wang JY, Man CX. Immunoregulatory effects on Caco-2 cells and mice of exopolysaccharides isolated from Lactobacillus acidophilus NCFM. *Food Funct* 2014; **5**: 3261-3268 [PMID: 25340590 DOI: 10.1039/c4fo00565a]
- 23 **Huang IF**, Lin IC, Liu PF, Cheng MF, Liu YC, Hsieh YD, Chen JJ, Chen CL, Chang HW, Shu CW. Lactobacillus acidophilus attenuates Salmonella-induced intestinal inflammation via TGF-β signaling. *BMC Microbiol* 2015; **15**: 203 [PMID: 26446848 DOI: 10.1186/s12866-015-0546-x]
- 24 **Elawadli I**, Brisbin JT, Mallard BA, Griffiths MW, Corredig M, Sharif S. Differential effects of lactobacilli on activation and maturation of mouse dendritic cells. *Benef Microbes* 2014; **5**: 323-334 [PMID: 24913839 DOI: 10.3920/BM2013.0066]
- 25 **Walker NM**, Simpson JE, Yen PF, Gill RK, Rigsby EV, Brazill JM, Dudeja PK, Schweinfest CW, Clarke LL. Down-regulated in adenoma Cl/HCO3 exchanger couples with Na/H exchanger 3 for NaCl absorption in murine small intestine. *Gastroenterology* 2008; **135**: 1645-1653.e3 [PMID: 18930060 DOI: 10.1053/j.gastro.2008.07.083]
- 26 **Borthakur A**, Gill RK, Tyagi S, Koutsouris A, Alrefai WA, Hecht GA, Ramaswamy K, Dudeja PK. The probiotic Lactobacillus acidophilus stimulates chloride/hydroxyl exchange activity in human intestinal epithelial cells. *J Nutr* 2008; **138**: 1355-1359 [PMID: 18567760]
- 27 **Singh V**, Raheja G, Borthakur A, Kumar A, Gill RK, Alakkam A, Malakooti J, Dudeja PK. Lactobacillus acidophilus upregulates intestinal NHE3 expression and function. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**: G1393-G1401 [PMID: 23086913 DOI: 10.1152/ajpgi.00345.2012]
- 28 **Chen CC**, Louie S, Shi HN, Walker WA. Preinoculation with the probiotic Lactobacillus acidophilus early in life effectively

- inhibits murine *Citrobacter rodentium* colitis. *Pediatr Res* 2005; **58**: 1185-1191 [PMID: 16306191 DOI: 10.1203/01.pdr.0000183660.39116.83]
- 29 **Schroder K**, Tschopp J. The inflammasomes. *Cell* 2010; **140**: 821-832 [PMID: 20303873 DOI: 10.1016/j.cell.2010.01.040]
- 30 **Mudter J**, Neurath MF. IL-6 signaling in inflammatory bowel disease: pathophysiological role and clinical relevance. *Inflamm Bowel Dis* 2007; **13**: 1016-1023 [PMID: 17476678 DOI: 10.1002/ibd.20148]
- 31 **Sang LX**, Chang B, Wang BY, Liu WX, Jiang M. Live and heat-killed probiotic: effects on chronic experimental colitis induced by dextran sulfate sodium (DSS) in rats. *Int J Clin Exp Med* 2015; **8**: 20072-20078 [PMID: 26884919]
- 32 **Chen L**, Zou Y, Peng J, Lu F, Yin Y, Li F, Yang J. *Lactobacillus acidophilus* suppresses colitis-associated activation of the IL-23/Th17 axis. *J Immunol Res* 2015; **2015**: 909514 [PMID: 25973440 DOI: 10.1155/2015/909514]
- 33 **Bulois P**, Tremaine WJ, Maunoury V, Gambiez L, Hafraoui S, Leteurtre L, Cortot A, Sandborn WJ, Colombel JF, Desreumaux P. Pouchitis is associated with mucosal imbalance between interleukin-8 and interleukin-10. *Inflamm Bowel Dis* 2000; **6**: 157-164 [PMID: 10961587]
- 34 **Visser YM**, Snel J, Zuurendonk PF, Smit BA, Wichers HJ, Savelkoul HF. Differential effects of *Lactobacillus acidophilus* and *Lactobacillus plantarum* strains on cytokine induction in human peripheral blood mononuclear cells. *FEMS Immunol Med Microbiol* 2010; **59**: 60-70 [PMID: 20337702 DOI: 10.1111/j.1574-695X.2010.00662.x]
- 35 **Chen LL**, Wang XH, Cui Y, Lian GH, Zhang J, Ouyang CH, Lu FG. Therapeutic effects of four strains of probiotics on experimental colitis in mice. *World J Gastroenterol* 2009; **15**: 321-327 [PMID: 19140231 DOI: 10.3748/wjg.15.321]
- 36 **Pan L**, Chen J, Yu J, Yu H, Zhang M. The structure of the PDZ3-SH3-GuK tandem of ZO-1 protein suggests a supramolecular organization of the membrane-associated guanylate kinase (MAGUK) family scaffold protein core. *J Biol Chem* 2011; **286**: 40069-40074 [PMID: 21965684 DOI: 10.1074/jbc.C111.293084]
- 37 **Shen ZY**, Zhang J, Song HL, Zheng WP. Bone-marrow mesenchymal stem cells reduce rat intestinal ischemia-reperfusion injury, ZO-1 downregulation and tight junction disruption via a TNF- $\alpha$ -regulated mechanism. *World J Gastroenterol* 2013; **19**: 3583-3595 [PMID: 23801859 DOI: 10.3748/wjg.v19.i23.3583]

P- Reviewer: Stanciu C S- Editor: Ma YJ L- Editor: Webster JR  
E- Editor: Li D







Published by **Baishideng Publishing Group Inc**  
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA  
Telephone: +1-925-223-8242  
Fax: +1-925-223-8243  
E-mail: [bpgooffice@wjgnet.com](mailto:bpgooffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>



ISSN 1007-9327

