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Evaluation the effect on ulcerative colitis of traditional Chinese medicine formula ya dan zi oil oral emulsion

Wei-ding Wang[1], Zi-cong Wu[1], Yi-fei Wang[2,3], Zhi-ping Wang[1*]

[1] Guangdong provincial engineering center of topical precise drug delivery system, School of Pharmacy,guangdong pharmaceutical University, Guangzhou 510006, China

[2] National Engineering Research Center For Modernazation Of Traditional Chinese Medicine-Ai Cao Sub Center,Guangzhou Jinan Biomedical Research and Development center, Guangzhou 510632,China

[3] Institute of biological medicine, jinan University, Guangzhou 510632, China

Wei-ding Wang and Zicong Wu contributed equally to this study. Wei-ding Wang is a pharmacy grade 17 undergraduate.

Abstract: **Ulcerative colitis(UC) is a chronic inflammatory disease affecting the colon, and its incidence is rising worldwide. Patients with ulcerative colitis have mucosal inflammation starting in the rectum that can extend continuously to proximal segments of the colon. Ulcerative colitis usually presents with bloody diarrhoea and is diagnosed by colonoscopy and histological findings. Ya dan zi oil oral emulsion(YDZ),a traditional Chinese medicine formula, composed of bruceae fructus(ya dan zi), is widely used as a clinically medication formula for its efficiency in cancers. But the underlying mechanisms by which it exerts therapeutic function of UC has not been thoroughly studied. In this study, acute ulcerative colitis was induced by oral administration of 2.5% dextran sodium sulfate for 7 days in drinking water, YDZ (12.0ml/kg body weight) decreased disease activity index and improved colon length at a certain degree, but compared with positive group(sulfasalazine) has no statistical significance.These results indicated that YDZ can hold protective effect on UC mice, but can not be used as a pharmaceutical preparations for UC treatments pontentionally.**

Keywords: Ya dan zi oil oral emulsion; Bruceae fructus; Ulcerative colitis

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1.Introduction

Ulcerative colitis (UC) is a chronic and relapsing inflammatory disorder of the colon and rectum with increasing morbidity in recent years, its symptoms include diarrhea and hematochezia[1,2]. In traditional Chinese medicine theory (TCM), UC is known as the"changpi" and chronic dysentery[3]. With the exception of patients who have a cecal patch, the inflammatory response usually begins in the rectum and extends proximally with a diffuse, continuous pattern. Characterized by chronic mucosal inflammation of the colon, UC presents with bloody diarrhea, tenesmus, abdominal pain, weight loss, fatigue, and even vomiting when symptoms become severe[4,5]. To date, UC remains one of the most challenging gastrointestinal diseases, impairing the quality of life and posing a high-risk threat of colorectal cancer in patients. The incidence and prevalence of UC have been reported to be on the rise over the past two decades [6]. Although the immunologic mechanism of UC has been postulated as an important participant in this disease, the etiology and pathophysiology are still unknown. Nowadays, the principal drugs for UC treatment are mainly consisted of four types: 5-aminosalicylic acid, steroid hormone, immunosuppressive agents and anti-tumor necrosis factor-α (anti-TNFα) drugs. However, serious side effects, such as easy to relapse, longterm medication side effects, refractory characteristics, limit their clinical application[7]. Therefore, it is of great significance to further understand the pathogenesis of UC and seek effective drugs for the treatment of UC.

Traditional Chinese medicine is one of alternative treatment options and has been increasingly recognized worldwide. Brucea javanica (L.) Merr. (Ya-dan-zi in Chinese) is an evergreen shrub and is widely distributed in Southeast Asia and northern Australia. Ya dan zi, an important Chinese medicinal herb, is used for treating dysentery, hemorrhoids, poisons cure, excrescence, corns and other diseases in Southeast Asia[8]. Ya dan zi oil oral emulsion(YDZ) is the fatty oil that is extracted from the desiccative ripe fruit of ya dan zi. It possesses various kinds of biological activities, such as anti-fungal, anti-oxidative, anti-inflammatory, and anti-cancer[9-12]. YDZ, a traditional Chinese medicine formula, composed of bruceae fructus(ya dan zi), is widely used as a clinically medication formula for its efficiency in cancers. But the underlying mechanisms by which it exerts therapeutic function of UC has not been thoroughly studied.

This study was designed to investigate the anti-inflammatory, antioxidant activity and protective effect on dextran sulfate sodium (DSS)-induced colitis mice of YDZ.

2.Material And Methods

Equipment

UV-visible spectrophotometer (UV2600, Shimadzu, kyoto, Japan); Ruler (SRL96080, M&G, Shanghai, China); Camera (ExmorRS, Sony, Tokyo, Japan).

Reagents

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Dextran sulfate sodium salt (DSS) produced by MP Biomedicals LLC (California, USA); San huang shu ai decoction (SH) was provided by Baiyunshan Xingqun Pharmaceutical Co. Ltd. (Guangzhou, Guangdong, China).

Animals

Male Balb/c mice (6–8 weeks, 18–22 g) were obtained from the Laboratory Animal Center of Southern Medical University (Guangdong, China) and group-housed under controlled temperature (22 ± 2 °C) and photoperiods (12 h: 12 h light–dark cycle). After the acclimation for 7 days, mice were matched by age and body weight. Care and experimentation of mice were performed in accordance with the Guide for the Care and Use of Laboratory Animals (Ministry of Science and Technology of China, 2006) and the related ethical regulations of China Pharmaceutical University.

Treatment protocol for DSS-induced colitic mice

UC mice was induced with 3% (w/v) DSS dissolved in drinking water continuously for 7 days, while the control group mice drank water without DSS (n = 6 mice in each group). SH (1.0 g/kg/d) and SASP (0.6 g/kg/d) were gavaged once a day from day 1 to day 8. Mice were observed once daily for weight, stool consistency, and the presence of gross blood in feces and at the anus. The DAI was calculated as previously described. On day 8, mice were executed, rapidly dissected, and the entire colons were quickly removed and took photos.

Statistical analysis

The results were expressed as mean ± standard deviation (SD) of three replicates. Statistical significance of data were analyzed by two-tailed Student's t test or one-way analysis of variance (ANOVA) followed by Dunnett's t-test. $P < 0.05$ was considered to be statistically significant and $P < 0.01$ was considered to be statistically very significant.

3.Result And Discussion

The chemical components of YDZ

The total components of YDZ were measured by GC-MS. As shown in Fig. 1, there were four components in YDZ: hexadecanoic acid (1,$C_{17}H_{34}O_2$, 8.81%), 9Z, 12Z-octadecadienoic acid (2, $C_{19}H_{34}O_2$, 19.53%), 9-octadecenoic acid (3, $C_{19}H_{38}O_2$, 62.68%), and heptadecanoic acid (4,$C_{18}H_{36}O_2$, 6.54%). Among the four components detected in this experiment, oleic acid and linoleic acid were identified as two major components, which was in line with previous investigation[13,14].

Effect of YDZ on clinical indices

In the animal model, 3% DSS in the drinking water induced marked symptoms as observed in human UC. No significant differences in body weight change were detected between groups at the beginning of the experiment. As shown in Fig. 2, the DAI score for the DSS group was significantly higher as compared to the control group ($P<0.01$). However, the DAI scores for the positive groups (SASP and AZA) and YDZ groups (BO-L, -M, -H) were significantly lower as compared to the DSS group ($P<0.01$), suggesting that the experimental colitis was suppressed significantly by the YDZ and positive control treatments. No significant differences in water and food intake were observed among all the DSS-treated groups in this study.

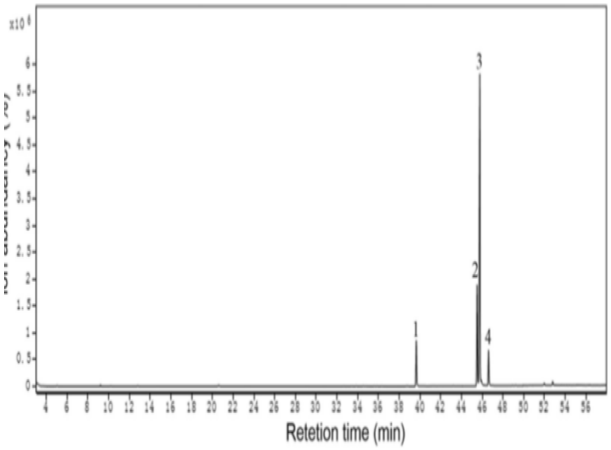

Fig. 1 Total contents of ya dan zi oil oral emulsion(YDZ).

The colon length is believed to be inversely associated with the severity of DSS-induced colitis. To determine whether YDZ had a beneficial effect on DSS-induced colonic shortening, we measured and compared the colon lengths of mice from different groups. Fig. 3 showed the photographs of the intestine in each group, and the colons of YDZ groups scarcely showed redness and swelling. However, the colons of mice in DSS group showed serious redness and bloody stools when compared with the normal group. The results indicated

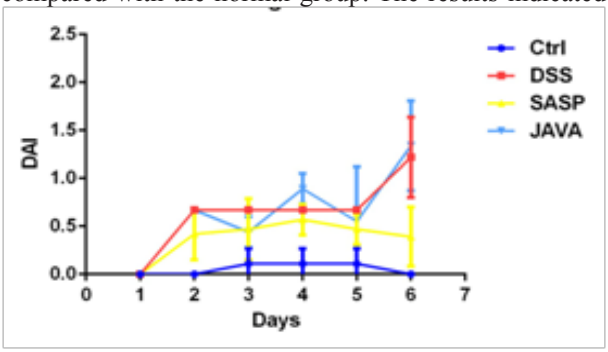

Fig. 2 The disease activity index (DAI) in mice. Data are compared between groups on the 8th day of the experiment and expressed as the means±S. E.M. of 15 mice in each group. #P<0.05, ##P<0.01 vs. normal control; *P<0.05, **P<0.01 vs. DSS group.

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that YDZ treatment, BOH in particular, could retain the colon length of DSS-induced mice.

4.Conclusion

In summary, our results indicated that YDZ the potential of anti-inflammation to treat UC induced by DSS as a promising candidate. Our research provided experimental evidence for the traditional application of ya dan zi in the treatment of dysentery and might extend the clinical indications for YDZ.

5.Discussion

Although UC is generally treated with anti-inflammatory or immunosuppressive agents, these

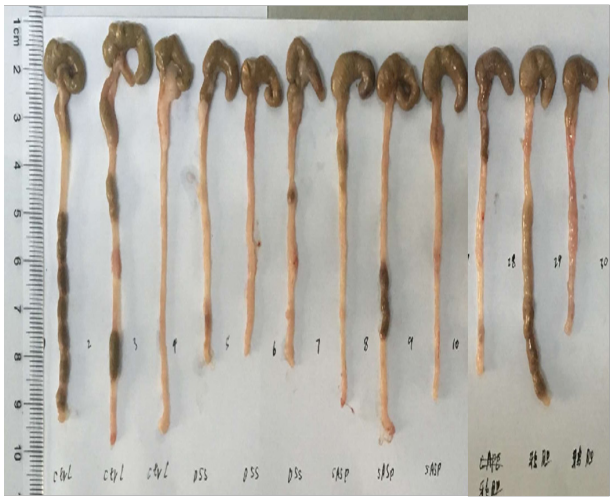

Fig. 3. Representative photographs of colon lengths.

therapies proved to be inadequate. Hence, many options have shifted to alternative therapies including TCM. In China, as the raw material of ya dan zi oil oral emulsion (YDZ), ya dan zi was traditionally used for the treatment of dysentery[15], which was also known as UC according to TCM theory [16]. Nowadays, the YDZ has been used widely in combination with conventional therapy to treat various kinds of cancers with favorable safety profile[17]. Current investigations on YDZ have been predominantly focused on its anticancer property, however, few e□orts have been contributed to the exploration of its major traditional application such as dysentery. Based on the ethnopharmacological use of ya dan zi, in the present work, we investigated the anti-inflammatory effect of YDZ on DSS-induced UC in Balb/C mice and elucidated the potential mechanism of action.

Reports indicate that ya dan zi is a complex mixture of fatty acids and fatty acid derivatives[18]. In the current work, the components of YDZ were determined by GC-MS, and it was found that oleic acid and linoleic acid were two major components among the four components detected, which was in accord with previous report [13]. Both of the two fatty acids have been reported to enhance the body immunity and also have been recognized as the indicative components for ya dan zi oil oral determination in pharmacokinetic and bioavailability studies on ya dan zi oil oral[14]. Furthermore, report indicated that oleic acid exerted anti-inflammatory effect in ameliorating the diabetic symptoms of type II diabetic mice characterized by inflammation [19].

Establishment of UC by oral administration of DSS in murine is a widely employed in vivo model for UC investigation, since the pathological alternations in this model closely resembles human UC[20]. Studies established that DSS-induced colitis was more representative of UC than TNBS-induced colitis, whose characteristics resemble human Crohn's disease (CD) [21]. Furthermore, DSS-induced colitis was characterized by focal crypt lesions, goblet cell loss and inflammatory cell infiltration at the areas of lesions, which was more intimately associated with inflammation as compared to other colitis models such as TNBS or oxazolone induced colitis model[22]. Hence, in the present work, DSS-induced colitis mice model was employed to investigate the potential anti-inflammatory effect and underlying mechanism of YDZ in the treatment of UC.

In this established model, we assessed DAI, colon length in DSS-induced Balb/c mice. The DAI scores represented the severity of DSS-induced colitis. High DAI score represented discomfort conditions of mice, including weight loss, faecal bleeding and diarrhea[23]. It was found that DSS-treated colitis mice exhibited higher DAI and shorter colon length as compared with the control. In contrast to the DSS group, mice treated with YDZ, SASP and AZA exhibited significantly attenuated a markedly reduced DAI after colitis induction. Colon length is an indirect index inversely related to the severity of DSS-induced UC. In this work, the colon length was observed to be remarkably recovered in mice of YDZ group. All the results above suggested that YDZE abrogated established colonic inflammation and had a noticeably protective effect against DSS-induced colitis in mice.

In the present work, to more comprehensively assess the effcacy of YDZ, we used positive drugs, namely sulfasalazine (SASP). SASP, which proved to be effective for treating UC, was a combination of 5-ASA azo-bound and the antibiotic sulfapyridine, which delivered a high concentration of 5-ASA to the colon[24]. In the present study, we found that SASP was effective in the treatment of UC. Furthermore, the therapeutic effect of YDZ was also proved to be pronounced. To the best of our knowledge, this study was the first endeavor to demonstrate the therapeutic effect of YDZ against DSS-induced murine experimental colitis, and

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reveal the potential mechanism of YDZ in regulating inflammation-associated events. This study showed that YDZ possessed appreciable anti-inflammatory effect in treating murine experimental UC induced by DSS. This investigation provided experimental evidence for the traditional application of ya dan zi in the treatment of dysentery, and might add new therapeutic dimensions to its current clinical application of YDZ and also provided a foundation and justification for further research as a potential complementary therapeutic agent to the current conventional medications.

6.Acknowledgements

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