Observational Study

Medicine®

OPEN

Therapeutic effects of *Ginkgo biloba* extract against acute ischemic colitis

Haiming Fang, MD[a,*], Chenhong Zhang, MB[a], Jiajia Wang, MD, PhD[b,*], Zhen Xu, MM[a], Cheng Qian, MB[a], Lijiu Zhang, MM[a]

Abstract

Ginkgo biloba extract (GBE) is a plant extract obtained from the leaves of *G biloba* tree. The aim of this study was to evaluate the clinicopathologic characteristics and therapeutic effects of GBE on ischemic colitis (IC).

Forty-seven patients with IC were divided as GBE group (n = 30) and routine group (n = 17). The routine group was given routine therapy, and the GBE group was given routine therapies plus GBE intravenous injection. Clinicopathologic characteristics, endoscopy findings, serum antioxidant enzymes, and inflammatory mediators were evaluated.

About 89.3% initial symptom was acute-onset abdominal cramping and abdominal pain followed with hematochezia. The lesions were mainly located in sigmoid colon (80.8%). Serum level of superoxide dismutase (SOD) in patients with IC was significantly decreased ($P < .05$), while methane dicarboxylic aldehyde (MDA), tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6) levels were significantly increased ($P < .05$). However, serum procalcitonin (PCT) level showed no significant change. Treatment of GBE resulted in quick remittance of abdominal pain and hematochezia, and significant attenuation of colon macroscopic and histologic damage in all patients. Furthermore, the treatment also significantly increased SOD levels, decreased MDA, TNF-α, and IL-6 levels ($P < .05$).

Acute-onset abdominal cramping or abdominal pain followed with hematochezia was the mainly initial symptom of IC, and sigmoid and descending colons were the common vulnerable sites. GBE exerted a beneficial effect on IC with faster symptom relief and better mucosal healing, possibly through scavenging oxidative-free radicals and downregulating inflammatory mediators. GBE may be a promising candidate for protection against IC.

Abbreviations: GBE = *Ginkgo biloba* extract, IC = ischemic colitis, IL-6 = interleukin-6, MDA = methane dicarboxylic aldehyde, NRS = numeric rating scale, PCT = procalcitonin, SOD = superoxide dismutase, TNF-α = tumor necrosis factor alpha.

Keywords: colonoscopy, *Ginkgo biloba* extract, interleukin-6, ischemic colitis, oxidative stress, pathology, procalcitonin, tumor necrosis factor alpha

1. Introduction

Ischemic colitis (IC) is the most common form of colonic ischemia, accounting for 50% to 60% of intestinal ischemia.[1] IC was first described as being caused by the ligation of the inferior mesenteric artery (IMA) during aortic reconstruction or colon resection.[2,3] Commonly, a sudden, temporary, diminished perfusion of colon could lead to ischemia, presenting with acute-onset abdominal pain and/or hematochezia.[4] The incidence of IC has risen from 6.1 cases/100,000 person-years in1976 to 1980 to 22.9/100,000 in 2005 to 2009.[5] The exact etiology and pathophysiology of IC are still unclear. As lack of specific clinical symptoms, and frequently confused intellectually with mesenteric ischemia and often misdiagnosed as infectious diarrhea or *Clostridium difficile* colitis.[6] How to detect early, diagnose early, and offer effective and timely therapy to IC are still a challenge.

Ginkgo biloba extract (GBE) is derived from *Ginkgo biloba* leaves. Standard GBE contains 22% to 27% flavonoids and 5% to 7% terpenoids, which are the most important active substances in the extract.[7] GBE has various biologic activities and different pharmacologic effects, including antioxidant properties, anti-inflammatory functions, and modulation of immune responses. GBE could dilate blood vessel and improve microcirculation in local tissues, which help prevent ischemic and reperfusion injury to tissue. Moreover, in patients with peripheral artery disease, GBE has been shown to improve pain-free walking distance.[8,9] For negligible side effects and low prices, GBE has been extensively used in the therapy of cardiovascular diseases and cerebral vascular ischemia/reperfusion injury in China and western countries.[7,10] Zhou et al[11] had found that GBE affected the release of inflammatory mediators in a dose-dependent manner, which resulted in a remarkable improvement of inflammatory injury in 2,4,6-trinitrobenzene sulfonic acid induced colitis in rats. GBE may be effective in the treatment of ulcerative colitis through its scavenging effect on oxygen-derived

Editor: Lei Huang.

This study was supported by the Doctor Fund of the Second Hospital of Anhui Medical University (no: 2012BKJ004).

The authors have no conflicts of interest to disclose.

[a] Department of Gastroenterology and Hepatology, The Second Hospital of Anhui Medical University, [b] Department of Pharmacology, Anhui Medical University, Hefei, Anhui Province, China.

[*] Correspondence: Jiajia Wang, Department of Pharmacology, Anhui Medical University, No 81 Meishan Road, Hefei, Anhui Province 230032, China (e-mail: wjj@ahmu.edu.cn); Haiming Fang, Department of Gastroenterology and Hepatology, The Second Hospital of Anhui Medical University, No 678 Furong Road, Hefei, Anhui Province 230601, China (e-mail: haimingfang@ahmu.edu.cn).

Medicine (2018) 97:35(e12166)

Received: 12 March 2018 / Accepted: 9 August 2018

http://dx.doi.org/10.1097/MD.0000000000012166

free radicals.[12] However, few literatures reported the effect of GBE on IC up to date. Thus, in the present study, we performed a retrospective analysis of clinicopathologic characteristics, endoscopy findings, and therapeutic effects of GBE on patients with IC, to further improve understanding of the disease features, and reduce the misdiagnosis and missed diagnosis.

2. Materials and methods

2.1. Populations

2.1.1. Inclusion criteria. From April 2010 to March 2016, patients with IC, admitted to Department of Gastroenterology and Hepatology, the Second Hospital of Anhui Medical University (Hefei, China), were enrolled in this study. This study was approved by the ethics committee of the Second Hospital of Anhui Medical University, and all subjects provided written informed consents.

2.2. Exclusion criteria

Patients were excluded who suffered from acute infectious enteritis or cannot tolerate colonoscopy because of severe diseases.

2.2.1. Laboratory tests and auxiliary examination. Routine laboratory examination included routine tests of blood, stool and urine, plasma glucose, cholesterol, triglyceride levels, liver function, thrombosis, and clotting series test. All patients obtained abdominal CT scans within 24 hours after admission and achieved successful colonoscopy and parallel mucosal biopsy examination within 72 hours after admission (Pentax CF-260I, Tokyo, Japan).

2.3. Diagnosis and grouping of IC

The diagnosis of IC was made as the following criteria [13–15]: acute-onset of abdominal symptoms such as abdominal cramping, abdominal pain followed with hematochezia; the presence of endoscopic findings consistent with IC; and the presence of histologic findings in biopsy specimens consistent with IC. Exclusion criteria included a medical history of inflammatory bowel diseases, colorectal cancer, stenosis, and obstruction of the gastrointestinal tract.

After IC was diagnosed, a total of 47 patients were finally deemed to satisfy the inclusion criteria and were divided into 2 groups as the GBE group (n = 30) and routine group (n = 17) randomly. Ten healthy volunteers with matching age and sex to the patients with IC were used as the normal group.

2.4. Treatment of IC and samples collection

After IC was diagnosed, patients in routine group were obtained routine therapies including intravenous fluid resuscitation, oxygen supplement, and fluoroquinolones combined with metronidazole or ornidazole. Patients in the GBE group were obtained intravenous injection of GBE twice daily for 7 days besides the above-mentioned routine therapy.

A 5 mL of peripheral blood sample was collected from each patient in the 2 groups before and after the 7 days treatment, respectively. Plasma samples were obtained and stored at −20°C until assayed. All patients obtained a repeated colonoscopy on day 8, and colon tissues were collected for analyses after 7 days treatment.

2.5. Clinical and safety assessment

Severity ratings of abdominal pain were scored by numeric rating scale (NRS), respectively: 0 = no abdominal pains, 1 to 3 = mild abdominal pains, 4 to 6 = middle abdominal pains, 7 to 10 = severe abdominal pains. Severity of abdominal discomfort was also according to the above NRS criteria. Abdominal pain, abdominal discomfort, and numbers of hematochezia were recorded in detail before and after treatment.

The clinicopathologic characteristics, endoscopy findings, and therapeutic effects of GBE were retrospectively analyzed. Close monitoring continued to assess for fever, increasing leukocytosis, development of acidosis, increased abdominal pain, or tenderness.

2.6. Assessment of macroscopic and histologic damage

Colon tissues were placed in 10% formalin for histopathologic evaluation. To process for microscopic studies, 5-μm thick paraffin sections were stained in hematoxylin and eosin (H&E) and were evaluated in a blind randomized fashion by 2 pathologists. Macroscopic damage scores were assigned using the following criteria according to a previous literature[12]: 0 = no macroscopic changes; 1 = mucosal erythema only; 2 = mild mucosal edema, slight bleeding or small erosions; 3 = moderate edema, bleeding ulcers or erosions; 4 = severe ulceration, erosions, edema, and tissue necrosis. Histologic scores were assigned using the following criteria[11,16,17]: the infiltration of acute inflammatory cells: 0 = no, 1 = mild increasing, 2 = severe increasing; the infiltration of chronic inflammatory cells: 0 = no, 1 = mild increasing, 2 = severe increasing; the deposition of fibrotin protein: 0 = negative, 1 = positive; the submucosa edema: 0 = no, 1 = patchy like, 2 = fusion like; the epithelium necrosis: 0 = no, 1 = limiting, 2 = widening; the epithelium ulcer: 0 = negative, 1 = positive. The ulceration, inflammation, lesion, and fibrosis were scored and put together as a result ranging between the minimum of 0 and maximum of 10.

2.7. Serum methane dicarboxylic aldehyde, superoxide dismutase, tumor necrosis factor alpha, interleukin-6, and procalcitonin level determination

Serum levels of superoxide dismutase (SOD), methane dicarboxylic aldehyde (MDA), procalcitonin (PCT), tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6) were analyzed by enzyme-linked immunosorbent assay (Cayman Chemical Company, Ann Arbor) according to the manufacturer's instructions. The cytokines were measured in duplicate.

2.8. Statistical analysis

Quantitative data are expressed as mean ± standard deviation, and 1-way analysis of variance was used to assess the statistical significance of the differences. Comparison between the groups was made by analyzing data with post-hoc method and inter- and intra-group statistical difference was performed using Tukey test. Statistical significance was set at a level of $P < .05$.

3. Results

3.1. Initial symptoms of IC

Totally, 47 patients with IC were enrolled in this study, 12 males and 35 females at mean age of 65.8 years, 50% patients were

Table 1

Compare of clinical symptoms relief and macroscopic and histologic damage scores after GBE or routine treatment.

	Abdominal pains		Abdominal discomfort		Hematochezia		Macroscopic score		Histologic score	
Group	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment
GBE	3.60±1.31	0.13±0.53	3.13±1.54	0.13±0.53	3.67±1.84	0.07±0.24	3.53±0.68	2.33±0.95	7.23±1.65	4.43±1.27
Routine	3.76±2.13	1.00±1.41	2.94±2.16	0.59±0.71	3.71±1.72	0.41±0.71	3.41±0.79	3.23±0.83	7.05±1.71	5.29±1.31
F-value	0.09	9.78	0.12	7.43	0.00	5.82	0.30	10.53	0.11	4.83
P-value	.76	.00	.73	.00	.94	.02	.58	.00	.73	.03

GBE = *Ginkgo biloba* extract.

Inter- and intra-group statistical difference was analyzed using Tukey test.

under 65 years. About 89.3% (42/47) was acute-onset abdominal cramping and abdominal pain followed with hematochezia. And 4.3% (2/47) was only acute-onset abdominal pain and 6.4% (3/47) just painless hematochezia. Other symptoms included nausea/vomiting (31.9%, 15/47) and diarrhea (19.1%, 9/47). No patients had fever and sepsis.

According the NRS, pretreatment score of abdominal pains in GBE and routine group had no significantly difference ($P=.76$). Similarly, pretreatment scores of abdominal discomfort and hematochezia were also no significantly difference between the 2 groups (Table 1).

3.2. Laboratory tests of IC

Only 7 patients (4 in GBE group and 3 in routine group) had increased white blood cell number with the maximum value 18.22×10^9/L. No significant different was found between GBE and routine group. The rest patients in GBE and routine group had normal white blood cell count. By routine inspection after admission, red blood cells and white blood cells in stool were found under light microscope in 17 patients and pus cells were found in 2 patients within them. All results of liver function, renal function, and thrombosis and clotting series test were normal in the 2 groups.

3.3. Abdominal radiology of IC

A total of 47 patients had obtained abdominal CT scans. Forty-one patients were normal and only 6 patients were found having local bowel-wall thickening stiff in the left colon. No abnormal changes were found after ultrasound examination of mesenteric blood vessels.

As the most likely cause of IC is the localized, nonocclusive ischemia which is in association with small vessel diseases, and large vessel occlusion is hardly identified, angiography is rarely helpful in the workup of IC. Thus none of the patients obtained abdominal angiography.

3.4. Ischemic lesion sites of IC

All the patients underwent successful colonoscopy and parallel mucosal biopsy examination within 72 hours after admission.

The lesion was mainly located in separate or involving the sigmoid colon (80.8%, 38/47), separate or involving in ascending colon (57.4%, 27/47), transverse colon (17.0%, 8/47), and rectum (6.4%, 3/47) (Figs. 1 and 2).

3.5. Macroscopic and histologic lesions of IC

Macroscopic presentation of the IC revealed different levels of colonic mucosal hyperemia, edema, erosion, and ulceration and submucosal hemorrhage. There was no significant difference of pretreatment macroscopic score between GBE group and routine group ($P=.58$, as shown in Table 1).

Histopathologic H&E staining of ischemic segment of colon was obvious acute and chronic inflammatory cells infiltration and epithelium ulcer and necrosis. Pretreatment histologic score had no significant difference between GBE group and routine group ($P=.73$, as shown in Table 1).

3.6. Effects of GBE on symptoms relief and colon mucosal healing of IC

In routine group, 24 hours after routine treatment, 8 of 15 acute-onset abdominal pain patients obtained disappearance of abdominal pain and 7 patients obtained significant clinical remission, 6 of 14 acute-onset abdominal cramping patients obtained disappearance of abdominal discomfort and 8 patients obtained significant clinical remission, 11 of 16 hematochezia patients obtained disappearance of hematochezia and 5 patients obtained significant clinical remission. Compared with pretreatment, patients with IC can obtain significant symptoms relief after 7 days of routine treatment (Table 1).

In GBE group, 24 hours after routine plus GBE treatment, 26 of 29 acute-onset abdominal pain patients obtained disappearance of abdominal pain and 3 patients obtained significant clinical remission; 25 of 28 acute-onset abdominal cramping patients obtained disappearance of abdominal discomfort, and 3 patients obtained significant clinical remission; 27 of 29 hematochezia patients obtained disappearance of hematochezia and 2 patients obtained significant clinical remission. Compared with pretreatment, patients with IC can obtain significant symptoms relief after 7 days of routine plus GBE treatment. Compared with routine therapy, routine therapy plus GBE treatment could contain markedly faster symptom relief (Table 1).

On the 8th day, after the routine treatment or routine therapy plus GBE intravenous injection twice daily for 7 days, all patients both in the routine group and in GBE group had obtained a repeated colonoscopy with written informed consents. Through the repeated colonoscopy, findings showed that routine treatment could significantly improve the ischemic mucosa lesions. Treatment of routine therapy plus GBE could attenuate the ischemic mucosa lesions, minimize the ulceration area, and alleviate the colitis. Compared with routine group, the extent and severity of the histologic signs were significantly attenuated. The severity of gross lesion score was significantly reduced. Treatment of routine therapy plus GBE could contain faster symptom relief and better mucosal healing (Figs. 1 and 2, Table 1).

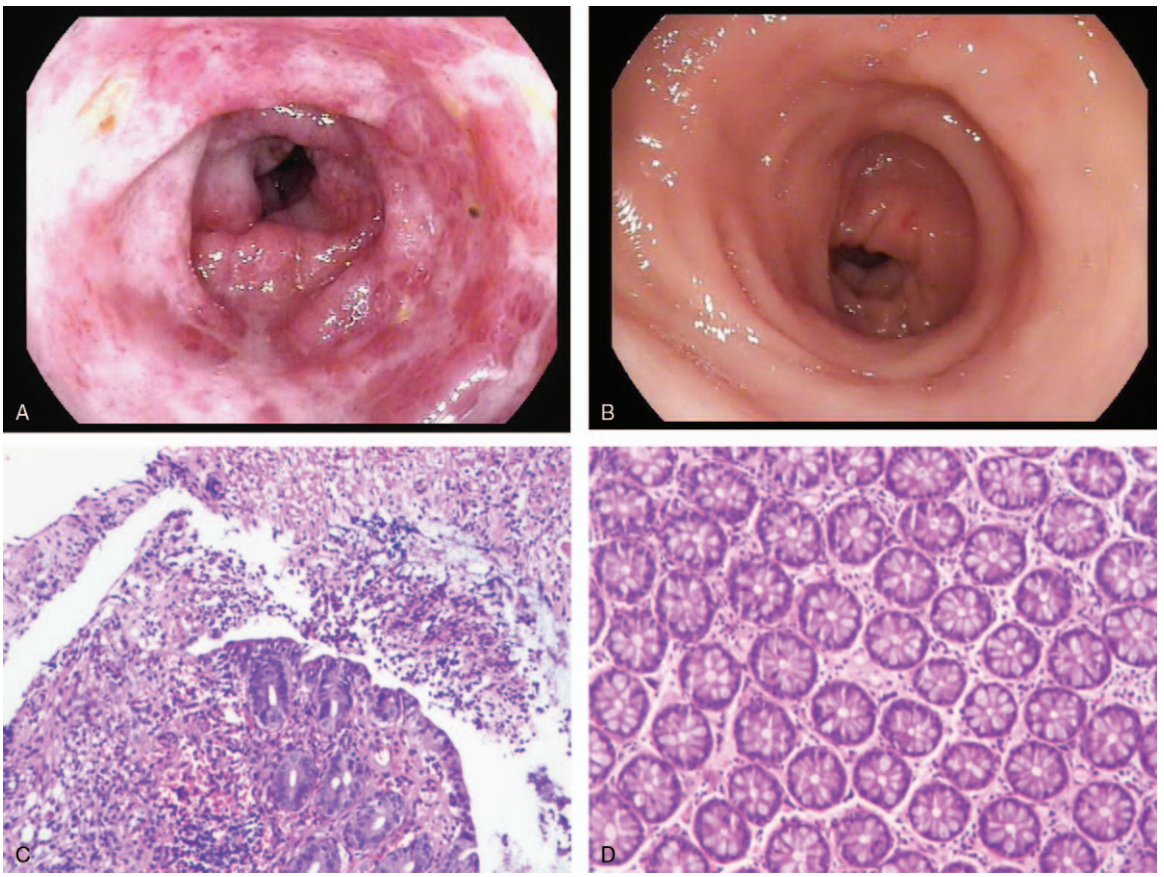

Figure 1. Endoscopic and histopathologic findings of an ischemic colitis (IC) patient and therapeutic effect of *Ginkgo biloba* extract (GBE). A: Serious lesion of sigmoid colon before GBE treatment with macroscopic damage score 4. B: Markedly improvement of lesion with nearly normal mucosa after GBE treatment. C: Histopathologic hematoxylin and eosin (H&E) staining before GBE treatment with histologic score 9. D: Histopathologic H&E staining after GBE treatment with histologic score 1.

3.7. Effects of GBE on serum MDA, SOD, TNF-α, IL-6, and PCT levels of IC

Compared with healthy volunteers, serum level of SOD in patients with IC was significantly decreased ($P < .05$), while MDA, TNF-α, and IL-6 levels were significantly increased ($P < .05$). However, serum PCT level showed no significant changes (Table 2).

Routine treatment to patients with IC, serum level of SOD was significantly increased ($P < .05$), and serum MDA, TNF-α, and IL-6 levels were significantly decreased, compared with pretreatment. Treatment of routine therapy plus GBE to patients with IC resulted in quick remittance of abdominal pain and hematochezia, and significant attenuation of colon macroscopic and histologic damage in all patients. Furthermore, the treatment also significantly increased SOD levels and decreased MDA, TNF-α, and IL-6 levels ($P < .05$) (Table 2).

4. Discussion

Ischemic bowel disease is an uncommon condition. Ischemic bowel disease can occur after vascular surgery or spontaneously resulted in insufficient blood supply to bowel, especially in the elderly with severe medical conditions.[6] Since the intestines are richly supplied with blood from abundant collateral circulation which is from the superior mesenteric artery (SMA) and the IMA. The rectum receives its blood supply from the paired internal iliac arteries and the IMA. Circulation from the SMA and IMA forms "watershed" areas of the colon, which is the most sensitive area to decreased blood flow. Because of this anatomical "watershed" area, colon is the most common region of ischemia in the gastrointestinal tract, and the splenic flexure and sigmoid colon are more likely to suffer from ischemia.[18] In the present study, the lesion was mainly located in sigmoid colon (80.8%) and descending colon (57.4%), which was consistent with reported literature.[19] These results further proved that anatomical vascular "watershed" area and insufficient blood flow of colon played a crucial role in the pathophysiology of IC.

As the temporary reduction of blood flow to the region of colon, ischemic changes subsequently extend from the mucosa to the serosa. Based on the degree of the IC, it is usually classified into 3 forms: gangrenous, stricturing, and transient. The clinical acute disease is divided into 2 groups: gangrenous colitis suffered from transmural necrosis and nongangrenous colitis, limited to the mucosa, or submucosa.[19] Serum PCT has been used as a reliable marker of bacterial infection. It is possible to differentiate bacterial infection from nonbacterial-related inflammation by measuring serum PCT levels.[20]

Numerous causes such as age over 65, hypertension, diabetes, hyperlipidemia, arrhythmia, chronic obstructive pulmonary disease, and hypercoagulable state are considered as major risk factors for IC.[21] Weather change and specific meteorologic factor may also be associated with IC onset. Kimura et al[22]

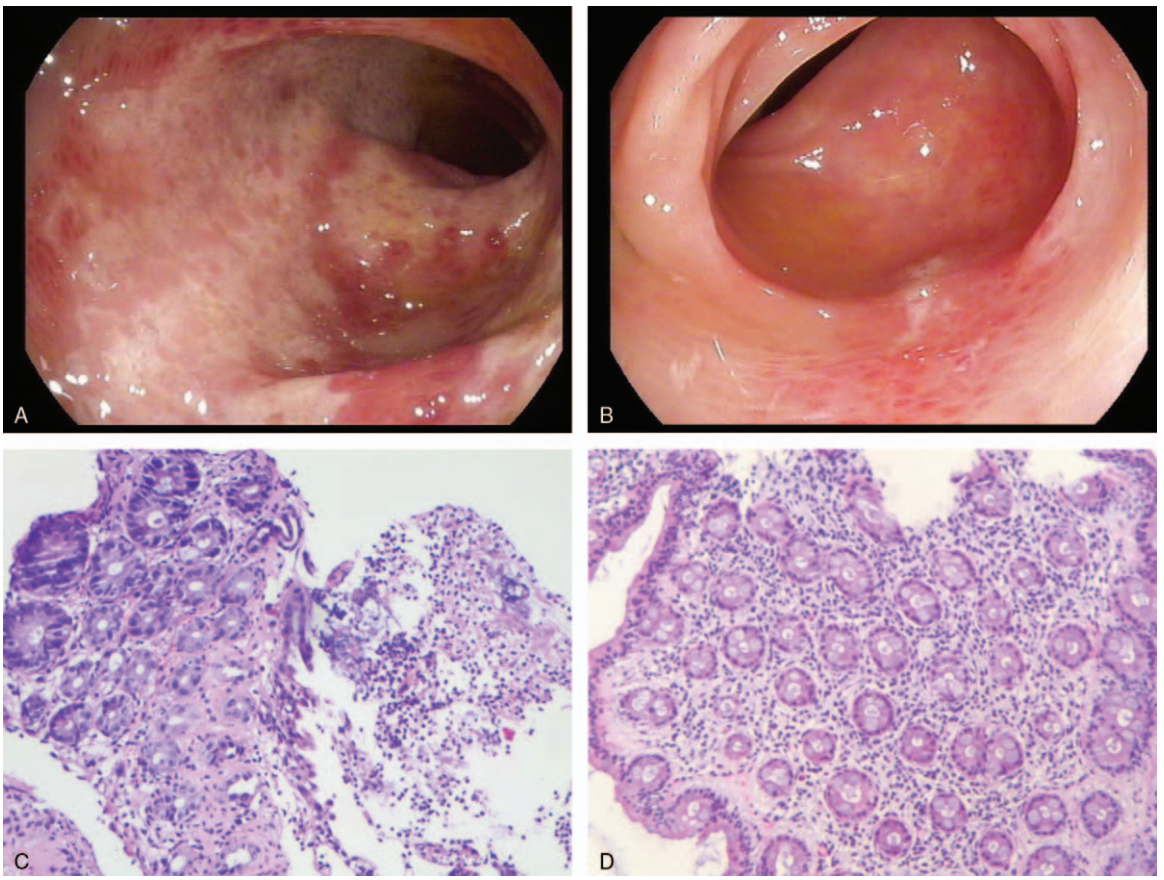

Figure 2. Endoscopic and histopathologic findings of a patient with ischemic colitis (IC) and therapeutic effect of routine treatment. A: Markedly lesion of sigmoid colon before routine treatment with damage score 3. B: Markedly improvement of the mucosal lesion after routine treatment with macroscopic damage score 2. C: Histopathologic hematoxylin and eosin (H&E) staining before routine treatment with histologic score 7. D: Histopathologic H&E staining after routine treatment with histologic score 3.

reported that lower air pressure and decrease in air pressure from the previous day are possible novel risk factors associated with the development of IC. In the present study, we found that about 36.7% (17/47) patients with IC had history of hypertension, 23.4% (11/47) patients had diabetes, and 14.9% (7/47) patients had coronary atherosclerotic heart disease. And nearly 70% patients with IC attacked in winter or spring season, especially in winter. These indicating that old patients with hypertension, diabetes, and/or coronary heart disease are vulnerable to IC, especially in cold weather.

Thrombus and coagulation test showed that no patients had hypercoagulable state in this study. Ultrasound examination of mesenteric blood vessels revealed no patients with mesenteric embolism or thrombosis. Abdominal CT scan revealed most were normal, and only several cases had local bowel-wall thickening stiff in the left colon. Serum PCT levels were mildly increased. These results indicated that all cases in the present study were nongangrenous colitis. None of them developed gangrenous colitis or multiple-system organ failure, and all of them were successfully managed nonoperatively.

Although IC was more frequent in the elderly, young people may also suffer IC.[23] About 50% of patients with IC occurred in people younger than 65 years old in this study. Of course, this needs further clinical epidemiology to prove. High prevalence of

Table 2

Effects of GBE the serum levels of MDA, SOD, TNF-α, IL-6, and PCT.

	SOD, U/L		MDA, nmol/L		PCT, ng/mL		IL-6, pg/mL		TNF-α, pg/mL	
Group	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment
Normal	20.42±4.18	–	3.88±0.79	–	0.04±0.02	–	5.75±2.99	–	0.05±0.03	–
GBE	12.57±4.46	18.15±5.89	6.25±1.89	4.71±2.70	0.08±0.03	0.06±0.04	108.40±66.27	26.34±22.10	0.11±0.04	0.08±0.02
Routine	11.64±4.94	14.31±4.60	6.44±1.98	5.72±1.53	0.07±0.02	0.06±0.04	111.06±50.78	88.50±33.23	0.10±0.04	0.09±0.05
F–value	0.42	4.11	0.10	6.60	0.02	0.01	0.02	73.62	0.44	1.06
P-value	.51	.04	.74	.01	.88	.91	.88	.00	.50	.03

IL-6 = interleukin 6, MDA = methane dicarboxylic aldehyde, PCT = procalcitonin, SOD = superoxide dismutase, TNF-α = tumor necrosis factor alpha.
Inter- and intra-group statistical difference was analyzed using Tukey test.

smoking habit and hyperuricemia are characteristic features of IC in the young adult population.[13]

Colonoscopy plays a vital role in the diagnosis and differential diagnosis of IC. In the present study, all patients acquired successful colonoscopy within 72 hours after admission. Once IC was suspected, early colonoscopy should be performed as soon as possible in clinical practices.

Oxidative stress (OS) and its consequent lipid peroxidation could aggravate free radical chain reactions and activate inflammatory mediators, which is a pivotal factor for local inflammation during inflammation processes. Excessive production of reactive oxygen species in mucosal cells could directly or indirectly cause damage of intestinal epithelial cells, subsequently influence mucosal integrity or initiate an inflammatory signaling cascade, and lead to severe impairment in colitis. The level of MDA was often used as an indication of oxidative damage and as a marker for free radical-induced lipid peroxidation. SOD, a primary defense, could reduce the oxidative stress and the activation of inflammatory mediators. In this study, we found that serum level of SOD was dwindled, and MDA level was increased remarkably in all IC cases, compared with healthy volunteers. These indicated that OS is regarded as an important aspect in the pathophysiology of ischemic and inflammatory diseases of the colon, consistent with previous literatures.[24,25]

Ginkgo biloba is one of ancient living tree species on earth. GBE is one of the most widely used herbal remedies. Indications of GBE include cardiovascular and cerebral vascular diseases, cognitive and dementia disorders, memory deficits, Alzheimer disease, depression, intermittent claudication, schizophrenia, and multi-infarct dementia.[26]

As known, anatomical vascular "watershed" area and insufficient blood flow of colon played a crucial role in the pathophysiology of IC. Fluid and electrolyte re-equilibration, and prevention of venous thromboembolism are important treatments for IC. Although GBE is a polyvalent radical scavenger, which improves mitochondrial function, decreases blood viscosity, and enhances microperfusion.[27] However few data reported on the effects of GBE on IC. In this study, patients with IC were treated with GBE for 7 days besides routine treatment, resulted in quick remittance of abdominal pain and hematochezia, significant attenuation of colon macroscopic, and histologic damage in all patients, and significant decreases of oxidative stress manifested by a marked increase in SOD and decrease in MDA. These results suggested that GBE provided protective effects in IC probably on the basis of its antioxidant activity and actions involving scavenging of free radicals and prevention of lipid peroxidation. GBE may be a potential effective therapeutic approach for the prevention against ischemic colon injury.

Leukocyte recruitment during inflammatory process caused regulated production of various pro- and anti-inflammatory mediators. Inflammatory mediators contribute to the inflammatory cascade in inflammatory diseases. TNF-α stimulated the synthesis of oxydative-free radicals, IL-6, IL-1, NO, and other inflammatory mediators, activated leukocytes, and promoted inflammatory cells migration in the intercellular matrix, all of which eventually amplified the inflammatory response by activating a cascade of immune cells. IL-6 is recognized for its role in the acute-phase inflammatory response, which is characterized by production of a variety of hepatic proteins termed acute-phase proteins, such as C-reactive protein and fibrinogen. Activation of the acute-phase response has been implicated in the pathogenesis of ischemic stroke. The expression of IL-6 is regulated mainly at the transcriptional level in neural cells.[28,29] In this study, consecutive treatment with GBE for 7 days resulted in a significant decrease in the serum level of TNF-α and IL-6, indicating that GBE had anti-inflammatory action in addition to its antioxidant properties. This findings were consistent with previous results in which GBE significantly reduced the expression of IL-6 at both the mRNA and protein levels in colon tissues in an experimental colitis rat model.[11]

Although literatures reported potential side effects of GBE such as gastrointestinal upset, headaches, dizziness, tinnitus, and bleeding. Systematic review and meta-analysis showed that there were no significant differences between GBE and placebo in participants experiencing any adverse events or serious adverse events. GBE has a good safety profile and is regarded as well tolerated in humans.[26,30] No patients suffered any side effects after achieved GBE treatment in the present study.

In summary, acute-onset abdominal cramping and abdominal pain followed with hematochezia is the main clinical features of IC. Sigmoid and ascending colon is the vulnerable site. Old patients with hypertension, diabetes, coronary heart disease chronic and/or obstructive pulmonary disease are vulnerable to IC, especially in cold weather. In routine clinical practice, when patients suffered abdominal pain followed with hematochezia, it is necessary to consider the possibility of IC and early colonoscopy should be performed as soon as possible. GBE exerted a beneficial effect on IC with faster symptom relief and better mucosal healing. As a possible mechanism, GBE could scavenge oxidative-free radicals, downregulate some of the inflammatory mediators involved in the intestinal immune, and inflammatory responses, including TNF-α and IL-6 resulting in the improvement of IC. GBE may be a promising candidate for protection against IC.

Of course, although we obtained some interesting findings of GBE on IC treatment, this is just a single center clinical observation. The mechanisms underlying these effects are also not entirely clear. More researches, especially multi-center clinical control trials are needed to identify safety, efficacy, and potential mechanism of GBE on IC.

Acknowledgment

The authors thank sincerely to Professor Yinguang Fan for his kindly help in the data statistics.

Author contributions

Conceptualization: Haiming Fang, Jiajia Wang.
Data curation: Haiming Fang, Chenhong Zhang, Jiajia Wang, Zhen Xu, Cheng Qian.
Formal analysis: Haiming Fang, Jiajia Wang.
Investigation: Chenhong Zhang, Cheng Qian.
Methodology: Haiming Fang, Jiajia Wang, Zhen Xu.
Project administration: Haiming Fang.
Software: Cheng Qian.
Supervision: Lijiu Zhang.
Writing – original draft: Haiming Fang, Jiajia Wang.
Writing – review & editing: Lijiu Zhang.

References

[1] Stamos MJ. Intestinal Ischemia and Infarction. 1995;WB Saunders, Philadelphia, PA:685–718.
[2] Shaw RS, Green TH. Massive mesenteric infarction following inferior mesenteric-artery ligation in resection of the colon for carcinoma. N Engl J Med 1953;248:890–1.

[3] Smith RF, Szilagyi DE. Ischemia of the colon as a complication in the surgery of the abdominal aorta. Arch Surg 1960;80:806–21.
[4] Brandt LJ, Feuerstadt P, Longstreth GF, et al. ACG clinical guideline: epidemiology, risk factors, patterns of presentation, diagnosis, and management of colon ischemia (CI). Am J Gastroenterol 2015;110:18–44.
[5] Yadav S, Dave M, Edakkanambeth Varayil J, et al. A population-based study of incidence, risk factors, clinical spectrum, and outcomes of ischemic colitis. Clin Gastroenterol Hepatol 2015;13:731–8.
[6] Tadros M, Majumder S, Birk JW. A review of ischemic colitis: is our clinical recognition and management adequate? Expert Rev Gastroenterol Hepatol 2013;7:605–13.
[7] Kleijnen J, Knipschild P. *Ginkgo biloba*. Lancet 1992;340:1136–9.
[8] Maerz S, Liu CH, Guo W, et al. Anti-ischaemic effects of bilobalide on neonatal rat cardiomyocytes and the involvement of the platelet-activating factor receptor. Biosci Rep 2011;31:439–47.
[9] Yan M, Liu YW, Shao W, et al. GBE761 improves histological and functional recovery in rats with acute spinal cord contusion injury. Spinal Cord 2016;54:259–65.
[10] Tian J, Liu Y, Chen K. *Ginkgo biloba* extract in vascular protection: molecular mechanisms and clinical applications. Curr Vasc Pharmacol 2017;15:532–48.
[11] Zhou YH, Yu JP, Liu YF, et al. Effects of *Ginkgo biloba* extract on inflammatory mediators (SOD, MDA, TNF-alpha, NF-kappaBp65, IL-6) in TNBS-induced colitis in rats. Mediators Inflamm 2006;2006:926–42.
[12] Mustafa A, El-Medany A, Hagar HH, et al. *Ginkgo biloba* attenuates mucosal damage in a rat model of ulcerative colitis. Pharmacol Res 2006;53:324–30.
[13] Kimura T, Shinji A, Horiuchi A, et al. Clinical characteristics of young-onset ischemic colitis. Dig Dis Sci 2012;57:1652–9.
[14] Moszkowicz D, Mariani A, Trésallet C, et al. Ischemic colitis: the ABCs of diagnosis and surgical management. J Visc Surg 2013;150:19–28.
[15] Matsumoto T, Iida M, Kimura Y, et al. Clinical features in young adult patients with ischaemic colitis. J Gastroenterol Hepatol 1994;9:572–5.
[16] Morris GP, Beck PL, Herridge MS, et al. Hapten-induced model of chronic inflammation and ulceration in the rat colon. Gastroenterology 1989;96:795–803.
[17] Mei Q, Yu JP, Xu JM, et al. Melatonin reduces colon immunological injury in rats by regulating activity of macrophages. Acta Pharmacol Sin 2002;23:882–6.
[18] Washington C, Carmichael JC. Management of ischemic colitis. Clin Colon Rectal Surg 2012;25:228–35.
[19] Marston A, Pheils MT, Thomas ML, et al. Ischaemic colitis. Gut 1966;7:1–5.
[20] Nagata J, Kobayashi M, Nishikimi N, et al. Serum procalcitonin (PCT) as a negative screening test for colonic ischemia after open abdominal aortic surgery. Eur J Vasc and Endovasc Surg 2008;35:694–7.
[21] Cubiella Fernández J, Núñez Calvo L, González Vázquez E, et al. Risk factors associated with the development of ischemic colitis. World J Gastroenterol 2010;16:4564–9.
[22] Kimura T, Shinji A, Tanaka N, et al. Association between lower air pressure and the onset of ischemic colitis: a case-control study. Eur J Gastroenterol Hepatol 2017;29:1071–8.
[23] Green BT, Tendler DA. Ischemic colitis: a clinical review. South Med J 2005;98:217–22.
[24] Bhattacharyya A, Chattopadhyay R, Mitra S, et al. Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases. Physiol Rev 2014;94:329–54.
[25] Thomson A, Hemphill D, Jeejeebhoy KN. Oxidative stress and antioxidants in intestinal disease. Dig Dis 1998;16:152–8.
[26] Diamond BJ, Bailey MR. *Ginkgo biloba*: indications, mechanisms, and safety. Psychiatr Clin North Am 2013;36:73–83.
[27] Tan MS, Yu JT, Tan CC, et al. Efficacy and adverse effects of *Ginkgo biloba* for cognitive impairment and dementia: a systematic review and meta-analysis. J Alzheimers Dis 2015;43:589–603.
[28] Costa G, Francisco V, Lopes MC, et al. Intracellular signaling pathways modulated by phenolic compounds: application for new anti-inflammatory drugs discovery. Cur Med Chem 2012;19:2876–900.
[29] Bukhari SN, Jantan I, Jasamai M. Anti-inflammatory trends of 1, 3-diphenyl-2-propen-1-one derivatives. Mini Rev Med Chem 2013; 13:87–94.
[30] Heinonen T, Gaus W. Cross matching observations on toxicological and clinical data for the assessment of tolerability and safety of *Ginkgo biloba* leaf extract. Toxicology 2015;327:95–115.