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Chaiqin Chengqi Decoction decreases IL-6 levels in patients with acute pancreatitis*

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Abstract: Objective: In this paper, we investigated the effect of the traditional Chinese medicine Chaiqin Chengqi Decoction (CQCQD) on serum cytokines in acute pancreatitis (AP) patients. Methods: Peripheral blood samples from 107 AP patients were collected within the first 48 h of AP onset and on the 10th day of CQCQD treatment. Control samples were collected from 20 healthy individuals. Serum proinflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), and anti-inflammatory cytokines IL-10 and IL-1β receptor antagonist (IL-1ra) were examined using the Luminex 100 system. Results: Within the first 48 h of AP onset, IL-6 and IL-1ra levels in severe AP (SAP) patients were significantly higher than those in mild AP (MAP) patients, but IL-10 levels in SAP patients were significantly lower than those in MAP patients. Proinflammatory cytokine IL-6 was significantly decreased after CQCQD treatment (P<0.05), especially in SAP patients (n=25 of 36, P<0.05). The hospitalization time of SAP patients was shortened significantly when serum IL-6 decreased after CQCQD treatment (P<0.05). Conclusions: CQCQD decreased proinflammatory cytokine IL-6 levels in AP patients.

Key words: Acute pancreatitis, Cytokine, Chaiqin Chengqi Decoction (CQCQD)
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1 Introduction

Acute pancreatitis (AP) is a common abdominal disease with increasing incidence in recent decades. The morbidity and mortality of AP are determined largely by the extent of the inflammatory response, which is mediated by a variety of proinflammatory cytokines (such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)) and anti-inflammatory cytokines (such as IL-10 and the IL-1β receptor antagonist (IL-1ra)) (Norman, 1998). AP may develop into life-threatening severe AP (SAP) if a systemic inflammatory response and distant organ complications occur. Previous studies have indicated that local proinflammatory mediators, such as IL-6, induce the systemic inflammatory response (Chen *et al*., 1999; Mayer *et al*., 2000). Serum IL-6 is a specific and sensitive marker for distant organ complications of SAP (Chen *et al*., 1999; Pezzilli *et al*., 1999; Mayer *et al*., 2000). Anti-inflammatory mediators, such as IL-10 and IL-1ra, are significantly higher in AP, and they could possibly reduce the severity of AP and AP-associated organ failure (Norman *et al*., 1995; Rongione *et al*., 1997; Frossard *et al*., 2001).

Traditional Chinese medicine has been used successfully to treat AP in China. Previous studies in experimental animal models and patients with AP have indicated that traditional Chinese medicines (such as baicalin, emodin, and Qingyi decoction) inhibit pancreatic enzymes and inflammatory mediators

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(Gong *et al.*, 2002; Xue *et al.*, 2006; Zhang *et al.*, 2008). At the West China Hospital, Chaiqin Chengqi Decoction (CQCQD) has been used to treat AP and has shown a significant efficacy. After CQCQD treatment, the mortality rate of SAP is about 10% (Liu *et al.*, 2004). This rate is lower than that previously reported (Whitcomb, 2006). In clinical applications, the efficacy of CQCQD has been proven; however, its mechanism of action remains unclear. In the present study, peripheral blood samples from AP patients were collected to examine cytokine levels. Relationships between cytokine levels, CQCQD treatment, and clinicopathological features of AP were examined.

2 Materials and methods

Peripheral blood samples from 107 AP patients were collected at two time points: within the first 48 h of AP onset and on the 10th day of CQCQD treatment. Peripheral blood samples from 20 healthy humans were collected as controls. The AP samples were divided into mild AP (MAP) (n=71) and severe AP (SAP) (n=36) according to the diagnostic criteria of the International Symposium of AP (Atlanta, USA, in 1992) (Bradley, 1993) and the guidelines for management of AP from the World Conference on Gastroenterology (Bangkok, Thailand, in 2002) (WCOG, 2002). MAP has no functional impairment or local complication and responds well to supplementary fluid treatment. The severity scores for MAP were as follows: Ranson's score <3, acute physiology and chronic health evaluation II (APACHE II) score <8, or computed tomography (CT) grade A, B or C. SAP is characterized by at least one of the following: local complication of pancreatic necrosis, pseudocyst or infected pancreatic tissue, and/or functional impairment of other organs. The severity scores for SAP were as follows: Ranson's score ≥3, APACHE II score ≥8, or CT grade D or E.

AP patients were divided into the following four subgroups: gallstone, alcohol, fat diet, and idiopathic. Clinical features of the subgroups differed. The gallstone AP group presented with cholelithiasis or biliary dilation on gallbladder ultrasound. The alcohol AP group had a history of episodes of binge drinking. The fat diet AP group had a history of eating a profusely fat diet before their AP symptoms appeared. Lastly, the idiopathic AP group included AP patients who had no identifiable underlying cause. MAP, SAP and control participants were on average (45.91±2.20), (50.63±5.15) and (51.33±12.01) years old, respectively. The mean hospitalization times for MAP and SAP patients were 18 and 26 d, respectively. All of the AP patients in this study have recovered. Peripheral blood samples were centrifuged to collect serum which was dispensed in 50 μl aliquots and stored at −20 °C before use. Clinicopathological information such as age, gender, patient history, hematological parameters, blood biochemistry analysis, and imaging results was collected. CQCQD was composed of Chaihu (bupleurum root) 15 g, Huangqin (baical skullcap root) 15 g, Houpu (magnolia bark) 12 g, Zhishi (immature orange fruit) 12 g, Shengdahuang (rhubarb) 20 g, and Mangxiao (Glauber's salt) 20 g. The composition was varied slightly according to an individual patient's conditions.

Concentrations of TNF-α, IL-6, IL-10, and IL-1ra were examined using LINCOplex, human cytokine/chemokine multiplex immunoassay kit (Missouri, USA Cat. No. HCYTO-60K-04, Kit ID No. HCYTO-53860/11806) and the Luminex 100 system (Austin, Texas, USA). The standard protocol for the process was followed. The concentrations of the four cytokines in each sample were calculated with a five-parameter model using Master QT software (Mirai-Bio, Alameda, CA, USA). The relationships between cytokine level and CQCQD treatment or clinicopathological features were analyzed using SPSS 13.0 software, with P<0.05 considered to be statistically significant.

3 Results

3.1 Relationships between cytokine levels and clinical pathological features

In the present study, four cytokines in peripheral blood samples were examined at the same time using Luminex, a process that has better reproducibility and sensitivity than traditional enzyme-linked immunosorbent assay (ELISA) (Biagini *et al*., 2004). The range of cytokine concentrations was from 10 to 10500 pg/ml. The R^2 of each cytokine's standard curve reached 0.997. In samples that were collected within the first 48 h of AP onset and without CQCQD

treatment, the relationships between cytokine levels and clinicopathological features were analyzed. The results showed that IL-6, IL-10 and IL-1ra levels were significantly higher in AP patients (P<0.05) than in healthy controls, and were correlated with the etiology and the severity of AP (P<0.05). No statistical differences in TNF-α were observed between AP patients and controls. The cytokine levels of different clinical etiological groups are shown in Table 1. Paired comparisons of the four AP subgroups showed that IL-10 levels of the fat diet and alcohol groups were significantly higher than those of the gallstone and idiopathic groups (P<0.05). IL-1ra levels of the fat diet group were significantly higher than those of the gallstone and alcohol groups (P<0.05). IL-6 levels of the alcohol group were significantly higher than those of the gallstone group (P<0.05). IL-6 levels of the fat diet group were significantly lower than those of the idiopathic group (P<0.05). Lastly, IL-6 and IL-1ra levels in SAP patients were significantly higher than those in MAP patients, but IL-10 levels in SAP patients were significantly lower than those in MAP patients (P<0.05) (Fig. 1).

Table 1 Cytokine level in each etiology group within the first 48 h of AP onset

Group	IL-10 (pg/ml)	IL-1ra (pg/ml)	IL-6 (pg/ml)
Gallstone (n=51)	9.37±2.76	234.72±42.87	38.18±18.27
Alcohol (n=16)	21.35±9.07$^{▲▼}$	286.98±58.61	126.26±62.41$^{▲}$
Idiopathic (n=31)	1.06±0.91	239.48±101.69	66.54±35.49
Fat diet (n=9)	24.35±12.27^{*Δ}	626.34±232.18$^{*#}$	20.56±9.28^{Δ}

Data are expressed as mean±SE. Paired comparisons of four groups: $^{▲}P$<0.05, alcohol group vs. gallstone group; $^{▼}P$<0.05, alcohol group vs. idiopathic group; $^{*}P$<0.05, fat diet group vs. gallstone group; ^{Δ}P<0.05, fat diet group vs. idiopathic group; $^{\#}P$<0.05, fat diet group vs. alcohol group

3.2 Effect of CQCQD treatment on cytokine levels of peripheral blood samples from AP patients

IL-6 and IL-10 levels were significantly decreased in AP patients after CQCQD treatment (P<0.05). Other cytokines were not significantly altered. In MAP and SAP patients, CQCQD treatment decreased different cytokines; IL-6 and IL-10 levels in MAP patients were significantly decreased (P<0.05, Fig. 2a), and IL-6 and IL-1ra levels in SAP patients were significantly decreased (P<0.05, Fig. 2b). TNF-α levels were significantly decreased following 10 d of treatment in SAP patients (n=25, (0.76±0.33) pg/ml vs. (3.59±1.49) pg/ml, P<0.05) and MAP patients (n=50, (0.11±0.08) pg/ml vs. (9.20±4.29) pg/ml, P<0.05) with significantly decreased IL-6.

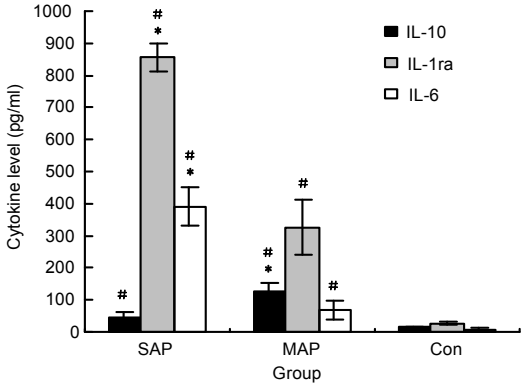

Fig. 1 Cytokine levels within the first 48 h of AP onset
Data are expressed as mean±SE. $^{\#}P$<0.05, AP vs. control; $^{*}P$<0.05, MAP vs. SAP

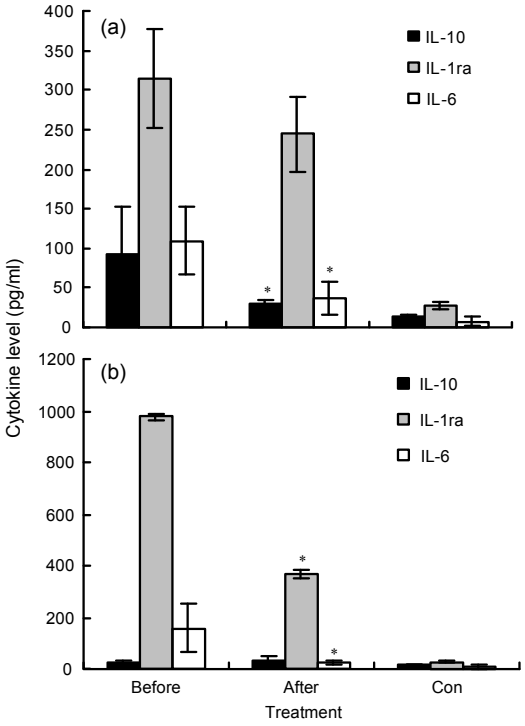

Fig. 2 Cytokine levels of MAP (a) and SAP (b) patients treated with CQCQD
Data are expressed as mean±SE. $^{*}P$<0.05, within the first 48 h of AP onset vs. the 10th day of CQCQD treatment

3.3 Effect of CQCQD treatment on hospitalization time of SAP patients

The hospitalization time of SAP patients was significantly shortened when serum IL-6 was decreased after CQCQD treatment (n=25, (31.6±8.2) d vs. (40.8±11.6) d, P<0.05). The hospitalization time of MAP patients did not significantly differ between patients with significantly decreased IL-6 (n=50) and other patients (n=21) ((15.8±3.7) d vs. (20.54±5.5) d, P>0.05).

4 Discussion

Previous studies have suggested that the proinflammatory cytokine IL-6 and anti-inflammatory cytokine IL-10 are sensitive markers for AP severity (Frossard *et al*., 2001; de Waele and Blot, 2007). In our study, proinflammatory cytokine IL-6 and anti-inflammatory cytokine IL-1ra were significantly higher in SAP patients than in MAP patients. This was consistent with previous reports (Hynninen *et al*., 1999; Mayer *et al*., 2000; de Waele and Blot, 2007), which showed that IL-6 and IL-1ra concentrations in the serum of SAP patients were significantly higher than those in MAP patients. Those studies indicated that IL-6 and IL-1ra were early markers of the severity of AP, and that IL-6 could be the best prognostic parameter for late complications. The serum value of IL-6 in the early stages of AP could be a more valuable prognostic indicator than those of other interleukins. Regarding IL-10, our finding contradicts some previous reports. Pezzilli *et al*. (1997) and Mayer *et al*. (2000) had shown that IL-10 concentrations in SAP patients were significantly higher than those in MAP patients. However, an experimental AP study in mice suggested that high concentrations of IL-10 could predict a mild form of the disease (Gloor *et al*., 1998). Several reasons for the discrepancy between the current findings and the past research are possible. First, cytokine concentrations in the present study were examined using the Luminex system. Using xMAP technology, the Luminex system can achieve higher sensitivity and accuracy (Biagini *et al*., 2004) than ELISA. Second, the patients in the present study were Chinese. Finally, our AP criteria were Atlanta (USA) and Thailand, which differed from the Balthazar criteria used by Pezzilli *et al*. (1997). In our study, we found no difference in TNF-α concentration between AP patients and healthy controls. One possible reason is that TNF-α clearance was rapid, even though it played a pivotal role in SAP and acted early in the course of AP.

CQCQD, a traditional Chinese medicine, has been used to treat AP for thousands of years with marked therapeutic effects. In previous studies, CQCQD has been found to reduce the mortality of SAP in clinical treatment (Wang *et al*., 2006). The mortality rate of SAP patients treated with CQCQD was 9.64% (Huang *et al*., 2003) compared with 15.6% for those treated without CQCQD (National Associated Group for Acute Pancreatitis, 2006). CQCQD's mechanism of therapeutic action in AP results mainly from its active components. CQCQD is composed of Chaihu (bupleurum root), Huangqin (baical skullcap root), Houpu (magnolia bark), Zhishi (immature orange fruit), Shengdahuang (rhubarb) and Mangxiao (Glauber's salt). The key active extracts of CQCQD components may be saikosaponin, baicalin, magnolol, honokiol, flavones, hesperidin, and emodin. In previous experimental animal studies, these active extracts have been found to play a part in anti-inflammation and in the induction of apoptosis through multiple pathways. These active components (such as saikosaponin, baicalin and emodin) might act by inhibiting nuclear factor kappa B (NF-κB), protein kinase C (PKC), or mitogen-activated protein kinase (MAPK) activation (Chao *et al*., 2010), thereby down-regulating inflammatory molecules such as TNF-α, IL-6, monocyte chemotactic protein-1 (MCP-1), nitric oxide (NO), and inducible NO synthase (iNOS) (Munroe *et al*., 2007; Yang *et al*., 2008; Zhang *et al*., 2008; Kuo *et al*., 2010) and increasing the anti-inflammatory cytokine IL-10 (Yang *et al*., 2008). Baicalin decreased plasma amylase, serum NO and TNF-α in a rat model of SAP (Zhang *et al*., 2008). SAP was found to involve extensive acinar cell necrosis but little acinar cell apoptosis (Bhatia, 2004). Experimental animal studies have shown that the induction of pancreatic acinar cell apoptosis protected mice against AP (Bhatia, 2004). The active components of CQCQD might induce apoptosis through increased Fas ligand, Bax, and Bak (Gong *et al*., 2002;

Pan *et al*., 2002; Hsu *et al*., 2004). Furthermore, the active components could have therapeutic effects on AP by reducing the release of pancreatic enzymes (Zhang *et al*., 2008), moderating cell necrosis, relieving the sphincter of Oddi spasms, protecting the intestinal mucosal barrier, and reducing other pathological damage to the pancreas (Yuan *et al*., 1997). In summary, the active components of CQCQD might be therapeutic because they decrease inflammation, induce apoptosis, and relieve other pathological damage.

In the present study, our results indicated that CQCQD regulated serum cytokine levels, decreasing the inflammatory response of AP patients. The proinflammatory mediator IL-6 was significantly decreased in all AP patients after treatment, especially in SAP patients. This decrease was consistent with the results from experimental animals treated with the active components of CQCQD (Munroe *et al.*, 2007; Yang *et al.*, 2008; Zhang *et al.*, 2008). However, the results of the anti-inflammatory cytokines changed after CQCQD treatment, a finding that was not consistent with previous experimental animal studies (Yang *et al.*, 2008). In our study, IL-10 levels in MAP patients and IL-1ra levels in SAP patients were significantly reduced by CQCQD treatment, whereas previous experimental animal studies had shown that anti-inflammatory IL-10 was increased by one active component of CQCQD (Yang *et al.*, 2008). The previous studies used only single active components, which have simpler effects compared with CQCQD (Munroe *et al.*, 2007; Yang *et al.*, 2008; Zhang *et al.*, 2008; Kuo *et al.*, 2010). Also, the previous studies were animal studies, whereas the current study used AP humans. The hospitalization time and TNF-α levels of SAP patients were decreased when serum IL-6 was significantly decreased by CQCQD. These results indicated that CQCQD might play a role in AP treatment by decreasing IL-6 levels. However, as we did not find that anti-inflammatory cytokine IL-10 and/or IL-1ra increased after CQCQD treatment, these results were contrary to our expectations. We had presumed that decreases in IL-10 or IL-1ra could result from decreased IL-6 (Steensberg *et al*., 2003). Steensberg *et al*. (2003) showed that IL-6 enhanced plasma IL-1ra and IL-10 in humans.

In the present study, we found that serum cytokine levels were correlated with the etiology of AP. These results suggest that different causes of AP can result in different inflammatory responses. Moreover, the digestion enzymes amylase and lipase were significantly higher in the gallstone group, compared to the alcohol and fat diet groups (data not shown). These results indicate that gallstones might promote pancreatic digestive enzyme secretion, which could then cause more serious local inflammation. However, proinflammatory cytokine levels of the gallstone AP patients were not the highest. The results indicated that cytokine concentrations of peripheral blood did not directly respond to local pancreatic inflammation. In the study, we found that the mean hospitalization time of gallstone patients was 26 d. This was longer than the hospitalization time of 16 and 18 d, respectively, of the alcohol and idiopathic AP patients. The hospitalization time of the fat diet group was the longest in the study, whereas proinflammatory cytokine IL-6 levels in that group were not significantly higher than the levels in the other groups. These results indicated that gentle inflammatory responses might be harmful during recuperation from AP. The different etiology groups had different cytokine levels. As the same treatment had different effects, the present findings suggest that AP etiology should be considered when selecting different therapeutic methods in clinical practice.

In summary, AP is a pancreatic inflammatory response mediated by a variety of proinflammatory cytokines and anti-inflammatory cytokines. In our study, proinflammatory cytokine IL-6 and anti-inflammatory cytokine IL-1ra were significantly higher in SAP patients, compared to MAP patients. CQCQD treatment decreased proinflammatory IL-6 levels in AP patients, especially in SAP patients, decreased the levels of anti-inflammatory IL-10 and IL-1ra in AP patients, and reduced the hospitalization time of SAP patients. CQCQD could be used selectively to treat SAP patients. The mechanisms underlying the therapeutic effect of CQCQD on AP patients, such as inducing apoptosis and relieving other pathological damage, should be considered in future research.

References

Bhatia, M., 2004. Apoptosis versus necrosis in acute pancreatitis. *Am. J. Physiol. Gastrointest. Liver Physiol.*, **286**(2):G189-G196.

Biagini, R.E., Sammons, D.L., Smith, J.P., MacKenzie, B.A., Striley, C.A., Semenova, V., Steward-Clark, E., Stamey, K., Freeman, A.E., Quinn, C.P., *et al*., 2004. Comparison of a multiplexed fluorescent covalent microsphere immunoassay and an enzyme-linked immunosorbent assay for measurement of human immunoglobulin G antibodies to anthrax toxins. *Clin. Vaccine Immunol.*, **11**(1):50-55. [doi:10.1128/CDLI.11.1.50-55.2004]

Bradley, E.L.3rd, 1993. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, Sept. 11 through 13, 1992. *Arch. Surg.*, **128**(5):586-590.

Chao, L.K., Liao, P.C., Ho, C.L., Wang, E.I., Chuang, C.C., Chiu, H.W., Hung, L.B., Hua, K.F., 2010. Anti-inflammatory bioactivities of honokiol through inhibition of protein kinase C, mitogen-activated protein kinase, and the NF-κB pathway to reduce LPS-induced TNFα and NO expression. *J. Agric. Food Chem.*, **58**(6):3472-3478. [doi:10.1021/jf904207m]

Chen, C.C., Wang, S.S., Lee, F.Y., Chang, F.Y., Lee, S.D., 1999. Proinflammatory cytokines in early assessment of the prognosis of acute pancreatitis. *Am. J. Gastroenterol.*, **94**(1):213-218. [doi:10.1111/j.1572-0241.1999.00709.x]

de Waele, J.J., Blot, S., 2007. The value of IL-6 in predicting the severity of acute pancreatitis. *J. Clin. Gastroenterol.*, **41**(5):534. [doi:10.1097/01.mcg.0000225522.43783.4b]

Frossard, J.L., Hadengue, A., Pastor, C.M., 2001. New serum markers for the detection of severe acute pancreatitis in humans. *Am. J. Respir. Crit. Care Med.*, **164**(1):162-170.

Gloor, B., Todd, K.E., Lane, J.S., Rigberg, D.A., Reber, H.A., 1998. Mechanism of increased lung injury after acute pancreatitis in IL-10 knockout mice. *J. Surg. Res.*, **80**(1):110-114. [doi:10.1006/jsre.1997.5289]

Gong, Z., Yuan, Y., Lou, K., Tu, S., Zhai, Z., Xu, J., 2002. Mechanisms of Chinese herb emodin and somatostatin analogs on pancreatic regeneration in acute pancreatitis in rats. *Pancreas*, **25**(2):154-160. [doi:10.1097/00006676-200208000-00007]

Hsu, Y.L., Kuo, P.L., Lin, C.C., 2004. The proliferative inhibition and apoptotic mechanism of Saikosaponin D in human non-small cell lung cancer A549 cells. *Life Sci.*, **75**(10):1231-1242. [doi:10.1016/j.lfs.2004.03.008]

Huang, Z.W., Xia, Q., Chen, G.Y., Tang, W.F., Xie, S.Y., Zhao, J.L., Jiang, J.M., 2003. Clinical therapeutic effects analysis of an early application of Chaiqin Chengqi Decoction in treating severe acute pancreatitis. *J. Chengdu Univ. TCM*, **26**(3):25-26 (in Chinese).

Hynninen, M., Valtonen, M., Markkanen, H., Vaara, M., Kuusela, P., Jousela, I., Piilonen, A., Takkunen, O., 1999. Interleukin-1 receptor antagonist and E-selectin concentrations: a comparison in patients with severe acute pancreatitis and severe sepsis. *J. Crit. Care*, **14**(2):63-68. [doi:10.1016/S0883-9441(99)90015-1]

Kuo, D.H., Lai, Y.S., Lo, C.Y., Cheng, A.C., Wu, H., Pan, M.H., 2010. Inhibitory effect of magnolol on TPA-induced skin inflammation and tumor promotion in mice. *J. Agric. Food Chem.*, **58**(9):5777-5783. [doi:10.1021/jf100601r]

Liu, X.B., Jiang, J.M., Huang, Z.W., Tian, B.L., Hu, W.M., Xia, Q., Chen, G.Y., Li, Q.S., Yuan, C.X., Luo, C.X., *et al*., 2004. Clinical study on the treatment of severe acute pancreatitis by integrated traditional Chinese medicine and Western medicine. *J. Sichuan Univ. (Med. Sci. Ed.)*, **35**(2):204-208 (in Chinese).

Mayer, J., Rau, B., Gansauge, F., Beger, H.G., 2000. Inflammatory mediators in human acute pancreatitis: clinical and pathophysiological implications. *Gut*, **47**(4):546-552. [doi:10.1136/gut.47.4.546]

Munroe, M.E., Arbiser, J.L., Bishop, G.A., 2007. Honokiol, a natural plant product, inhibits inflammatory signals and alleviates inflammatory arthritis. *J. Immunol.*, **179**(2):753-763.

National Associated Group for Acute Pancreatitis, 2006. Etiology and mortality of acute pancreatitis in China: analysis of 6223 clinical cases. *Clin. J. Pancreatol.*, **6**(6):321-325.

Norman, J., 1998. The role of cytokines in the pathogenesis of acute pancreatitis. *Am. J. Surg.*, **175**(1):76-83. [doi:10.1016/S0002-9610(97)00240-7]

Norman, J.G., Franz, M.G., Fink, G.S., Messina, J., Fabri, P.J., Gower, W.R., Carey, L.C., 1995. Decreased mortality of severe acute pancreatitis after proximal cytokine blockade. *Ann. Surg.*, **221**(6):625-634. [doi:10.1097/00000658-199506000-00002]

Pan, L., Yuan, Y.Z., Zhang, Y.P., Qiao, M.M., Zhai, Z.K., 2002. Mechanisms of emodin in apoptosis of pancreatic cells in acute pancreatitis in rats. *Clin. J. Pancreatol.*, **12**(2):214-217.

Pezzilli, R., Billi, P., Miniero, R., Barakat, B., 1997. Serum interleukin 10 in human acute pancreatitis. *Dig. Dis. Sci.*, **42**(7):1469-1472. [doi:10.1023/A:1018814710291]

Pezzilli, R., Morselli-Labate, A.M., Miniero, R., Barakat, B., Fiocchi, M., Cappelletti, O., 1999. Simultaneous serum assays of lipase and interleukin-6 for early diagnosis and prognosis of acute pancreatitis. *Clin. Chem.*, **45**(10):1762-1767.

Rongione, A.J., Kusske, A.M., Kwan, K., Ashley, S.W., Reber, H.A., McFadden, D.W., 1997. Interleukin 10 reduces the severity of acute pancreatitis in rats. *Gastroenterology*, **112**(3):960-967. [doi:10.1053/gast.1997.v112.pm9041259]

Steensberg, A., Fischer, C.P., Keller, C., Møller, K., Pedersen, B.K., 2003. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *Am. J. Physiol. Endocrinol. Metab.*, **285**(2):E433-E437.

Wang, Z.C., Xue, P., Huang, Z.W., You, Z., Guo, J., 2006. Clinical study of severe acute pancreatitis complicating with acute respiratory distress syndrome treated by

Chaiqin Chengqi Decoction in early stage. *Chin. J. Curr. Tradit. West. Med.*, **4**(10):874-876 (in Chinese).

WCOG, 2002. Quadrennial reviews and working party reports from the World Congress in Gastroenterology. February 24-March 1, 2002. Bangkok, Thailand. *J. Gastroenterol. Hepatol.*, **17**(s1):S1-S195.

Whitcomb, D.C., 2006. Clinical practice. Acute pancreatitis. *N. Engl. J. Med.*, **354**(20):2142-2150. [doi:10.1056/NEJMcp054958]

Xue, D., Zhang, W., Zhang, Y., Wang, H., Zheng, B., Shi, X., 2006. Adjusting effects of baicalin for nuclear factor-κB and tumor necrosis factor-α on rats with caerulein-induced acute pancreatitis. *Mediators Inflamm.*, **2006**(5):26295. [doi:10.1155/MI/2006/26295]

Yang, T.C., Zhang, S.W., Sun, L.N., Wang, H., Ren, A.M., 2008. Magnolol attenuates sepsis-induced gastrointestinal dysmotility in rats by modulating inflammatory mediators. *World J. Gastroenterol.*, **14**(48):7353-7360. [doi:10.3748/wjg.14.7353]

Yuan, Y.Z., Wu, J.X., Xu, J.Y., 1997. Effects of emodin and stilamin on abnormal metabolism of eicosanoids in acute haemorrhagic-necrotizing pancreatitis in rats. *Chin. J. Dig.*, **17**:274-276 (in Chinese).

Zhang, X.P., Zhang, L., Yang, P., Zhang, R.P., Cheng, Q.H., 2008. Protective effects of baicalin and octreotide on multiple organ injury in severe acute pancreatitis. *Dig. Dis. Sci.*, **53**(2):581-591. [doi:10.1007/s10620-007-9868-3]