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Review:

Study progress in therapeutic effects of traditional Chinese medicine monomer in severe acute pancreatitis*

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Abstract: Severe acute pancreatitis (SAP) is a common acute abdomen clinical problem characterized by high mortality, multiple complications, complicated pathogenesis and difficult treatment. Recent studies found traditional Chinese medicine (TCM) monomers have markedly good effect for treating SAP. Many TCM monomers can inhibit pancreatin, resist inflammation, improve microcirculation and immunoloregulation, etc. to block the pathological progress of SAP in multiple ways, reduce complications and lower mortality with rapid effects. It is significant for enhancing SAP treatment to deeply understand the current situation in TCM monomers for treating SAP and take precious references therein. This article summarizes the treating effects and mechanisms of TCM monomers for SAP in recent years.

Key words: Severe acute pancreatitis, Treatment, Traditional Chinese medicine (TCM) monomer
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INTRODUCTION

Severe acute pancreatitis (SAP) is one of the three main acute abdominal problems always accompanied by multiple-system and multiple-organ impaired function or failure. Its onset and development are characterized by rapid changes, complicated illness state and difficult treatment. With the continuous development of the traditional Chinese medicine industry in recent years, it is proved that traditional Chinese medicine (TCM) monomers monomers have a marked effect for treating SAP with unique advantages. Therefore this article has summarized the TCM monomers with marked therapeutic effects on SAP in recent years and demonstrated their treating effects and mechanisms.

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EXPERIMENTAL STUDY PROGRESS

Emodin

Emodin, an anthraquinone derivative extracted from rhubarb (*Rheum palmatum* L., *Rheum tanguticum* Maxim. ex Balf or *Rheum officinale Baill*) and free anthraquinone aglucone can lead to catharsis, serve as cholagogue, protect liver, resist infection, promote secretion of pancreatic fluid and pancreatin, etc. TGFβ1 mRNA expression was tested on rat acute pancreatitis models induced by intraperitoneal infusion of caerulein, treated or untreated by emodin (Lou *et al*., 2001). TGFβ1 mRNA expression was strongly detected at 6 h after treatment and reaching the peak at 48 h (move forward compared to the untreated group). The DNA synthesis and total protein content in pancreatic tissue also increased significantly in the emodin treated group, which indicated the mechanism of emodin in treating acute pancreatitis might be by way of enhancing cytokine TGFβ1 gene expression, regulating cell growth and differentiation,

stimulating the formation of extracellular matrix components, increasing DNA synthesis and protein content, and taking part in pancreatic repairing and remodeling. The expression of Bax mRNA was detected to increase significantly in SAP rats treated by emodin compared with the untreated ones, which indicated the therapeutic efficacy of emodin in the treatment of acute pancreatitis may be attributed to its action of modulating apoptosis-related genes (Pan *et al*., 2002). Wu *et al*.(1997) found emodin could markedly improve pancreatic ischemia in early stage of SAP, which may be due to inhibiting abnormal metabolism of gadoleic acid. Emodin can improve microcirculation and enhance cell protection, which is beneficial to SAP treatment. So, as a common medicine in treating SAP, emodin mainly can lead to catharsis, promote secretion of bilirubin and bile acid, relieve sphincter of Oddi spasm, eliminate oxygen free radicals, lower endotoxin level of plasma, effectively inhibit the abnormal metabolism of vasoactive substances such as gadoleic acid to improve microcirculation; It also can promote secretion of pancreatic fluid, interfere with function of apoptotic gene, induce acinar cell apoptosis of pancreas and thus avoid or reduce the release of pancreatin and inflammatory mediators to block pathogenic process (Gao and Chen, 1990).

Tripterygium glycosides

Tripterygium glycosides (TII), a glucoside preparation extracted from the root of Tripterygium wilfordii Hook. F, is a non-steroidal immunosuppressor. Its main component is diterpene lactone with relatively strong anti-inflammatory and immunosuppressive activities (Men, 1994). NF-κB is a transcription factor playing an important role in a series of immunological and inflammatory reactional genetic transcription. It has obvious inhibiting effect on T cell proliferation and the activity of mediators of inflammation, including IL-1, IL-6, IL-8 and TNFα and thus blocks the "waterfall" cascade effect of inflammatory mediators. SAP models induced by retrograde injection of 5% sodium taurocholate to the pancreatic duct were treated by intraperitoneal injection of TII (Zhang *et al*., 2005). Serum amylase, endotoxin level of plasma, IL-1, TNFα and NF-κB activity were significantly decreased and life span extended in the treated group compared with the untreated one. Suspension of TII powder was injected into 30 SAP rats intraperitoneally, 50 mg/(kg·d), 3 d or ended the administration upon death of animals (Jin *et al*., 2000). After treatment, amylase, endotoxin, TNF-α and IL-1 indexes dropped markedly, pancreas pathological grading by optical microscope dropped obviously, cell injury was reduced under electron microscope. The mechanism of TII treating SAP might be through inhibiting NF-κB activity, decreasing inflammatory mediator levels and reducing the pathological damage of the pancreas.

Ginkolide B

Ginkolide B which is the main active ingredient of extract from Ginkgo Biloba, EGb of Ginkgo family, is a terpene compound and natural platelet activating factor (PAF) antagonist with strong activity (Pietri *et al*., 1997). Flavone glycosides (24%) and lactone (6%) are two effective constituent of Ginkolide B. Flavone glycosides plays an important role in eliminating excessive oxygen free radicals in body, inhibiting the lipid peroxidation of cell membrane, enhancing the superoxide dismutase (SOD) activity of red cells and thus protecting cell membrane, preventing serious body injuries from free radicals. Lactone acts as a PAF antagonist and improves blood rheology, modulates neurotransmitter release, increases oxygen and glucose supply of ischemic tissues and lowers blood viscosity. Two randomized, double-blind, placebo-controlled trials (Schneider *et al*., 2005; Horsch and Walther, 2004) proved that EGb could improve cognitive performance of patients with Alzheimer's disease and the outcome of patients with peripheral arterial occlusive disease. Zeybek *et al*.(2003) found prophylactic application of EGb caused significant decrease in serum amylase and lipase levels compared with the control group. Yamaguchi *et al*.(1999) treated rats with EGb after inducing SAP by caerulin. Edema, leucocytes, amylase, pancreas weight and PAF concentration all changed markedly, while lucigenin, luminol, NO marks declined markedly. Treatment of SAP rats with EGb significantly reduced both frequency of bacterial translocation and intestinal mucosal cells apoptosis compared with the control group, which suggest EGb has protective effect on cell membrane, prevents serious body injuries from free radicals, improves microcirculation of pancreas and intestines and lowers endotoxin level (Zhang *et al*., 2004).

Sanchinoside

Sanchinoside extracted from *Panax notoginseng* (Fam. Araliaceae) is dammarane type triterpene saponin, mainly includes 9 kinds of monomers such as panaxoside Rb1, Rb2, Rc, Rd and Rg1. The hydrolysates of sanchinoside are panoxadiol (PDS) and panoxatriol (PTS). It can dilate blood vessel, improve microcirculation, protect anti-oxidation capacity of tissue, inhibit lipid peroxidation, reduce Ca^{2+} inflow, and affect generation of free radicals (Guan *et al*., 1990). Xiong *et al*.(2004) found sanchinoside could reduce the nitric oxide levels in plasma and pancreas in rats with acute necrotizing pancreatitis (ANP) (2~12 h after induction). Sanchinoside can inhibit the release of pancreatic amylase, inflammatory factor, cytokine and activate macrophage and T cells. SAP rats were treated by sanchinoside (20 mg/100 g) and somatostatin (1 μg/100 g) and put to death respectively after 2 h and 4 h. The pathological injury of pancreas tissue was markedly reduced, serum amylase, TXB2 and TNF-α level dropped markedly especially during early stage of function (Ge *et al*., 2002). Especially, sanchinoside showed more inhibitive efficacy on TXB2 and TNF-α compared with somatostatin group.

Taxol

Taxol, an extract from bark of torreya (Taxaceae) and diterpene compound has potent anti-cancer effect. It can induce apoptosis of pancreatic acinar cell and can be used to treat cancer by adjusting the contents of apoptosis-associated protein Bcl-2, Bax, Fas, FasL and p53. It can raise Bax level to promote acinar cell apoptosis, markedly elevate the expression of p53 protein which had declined during SAP, increase the expression of FasL mRNA and promote acinar cell apoptosis by increasing the Fas expression of acinar cell. The apoptosis promoting effect of taxol depends on dosage. There is a marked positive correlation between dose of taxol and pancreatic acinar cell apoptosis index within a relative small dose range. Which indicates in small doses, taxol tends to induce pancreatic acinar cell apoptosis and thus relieve the severity of the pancreatitis. But there is a marked negative correlation between dose of taxol and pancreatic histological changes within a relative high dose range, and increase of dose makes the signal channel of cell necrosis dominant and aggravates pancreatitis. Various taxol doses were given to the rats of SAP by intraperitoneal infusion, and checked the cell apoptosis index after 24 h (Chao and Qi, 2003). The result showed 5 mg/kg dose resulted in the most marked effect and minimum necrosis of the acinus. The treating effect declines with the increase or decrease of the dosage.

Resveratrol

Resveratrol, an extract from dried giant knotweed rhizome (polygonaceae) and hydroxyl diphenyl ethylene extensively distributed in the vegetable kingdom can resist inflammation, oxidation, platelet aggregation, etc. Resveratrol can inhibit the generation, activation and release of inflammatory mediators: it can reduce the generation of NO, IL-1, IL-6, TNF, etc. during inflammatory process by inhibiting the NF-κB activation of macrophage, lymphocyte, etc., block NF-κB activation induced by TNF, and inhibit mitogen caused protein kinase activation induced by TNF. After 90 rats were randomly divided into 5 groups, including blank control group and treatment groups, determinations were conducted respectively at 3, 6, 12 h and the result showed resveratrol can inhibit the serum IL-6 and TNF level of SAP rat model at dosage of 10 mg/kg, and reduce the generation of inflammatory mediators of acute pancreatitis and mortality (Huang *et al*., 2005).

Rutoside

Rutoside (Ru), the main extract and flavonol from bud of Chinese scholar tree (Leguminosae) can resist inflammation, reduce capillary fragility and resist oxidation. In AP (acute pancreatitis) pancreatic tissues, the expression of inducible nitric oxide synthase (iNOS) increases. In inflammatory reactions, the activity of iNOS and NO level increase abnormally leading to systemic hemodynamic disturbance and lipid peroxidation injury. Rats were randomly divided into 5 groups, including control group, model group and three Ru treatment groups with different doses (Tian *et al*., 2006). Ru was injected subcutaneously at posterior limb and determined after 24 h. The serum amylase (AMS) of rats in treatment group dropped markedly and edema in pancreatic tissues was markedly alleviated. It effectively lowers elevated serum NO level, enhances SOD (superoxide dismutase) activity and reduces MDA (malondial-

dehyde) generation. Ru can also effectively inhibit the activity of type II phosphatidase A_2 (II PLA_2). Ru (60, 120 mg/kg) increases serum Ca^{2+} concentrations after the induction of AP at 6 and 12 h and decreases Ca^{2+} concentrations of pancreas tissue and significantly raises PLA_2 levels after the induction of AP at 24 h. The study indicated that the mechanisms of protective effect of Ru on the experimental AP might block the translocation of calcium from extracellular to intracellular compartments and attenuate the injury of Ca^{2+} overload in acinus. And possibly, the antagonistic effect is also related to the inhibition on PLA_2 activation.

CLINICAL TREATMENT PROGRESS

Anisodamine

Anisodamine also named 654-2 is alkaloid extracted from Anisodus Tonguticus. As acetylcholine receptor antagonist, anisodamine can block M and α receptor, improve metabolism of arachidonic acid, relieve vascular smooth muscle spasm, lower vascular resistance, modulate calcium homeostasis, block Ca^{2+} inflow, effectively stop cell calcium overload in ischemia reperfusion injury, increase energy and oxygen supply of tissue, protect cells at cell level, enhance their tolerance to ischemia and hypoxidosis, stabilize lysosome membrane of gland cells, and thus block the activation and occurrence of pancreatin, evolution of self digestion in early stage, inhibit pancreas gland secretion and let pancreas glands with pathological changes rest and recover (Yu and Tan, 1992). In addition, it also can resist oxygen free radicals and endotoxin at cell membrane level, etc. (Tang, 1986). Ma *et al*.(2003) randomly divided 60 cases of hospitalized SAP patients into two groups, and the treatment group was given anisodamine 40~100 mg, intravenously continuously each day and yielded distinct treatment effects. Finally, there was marked statistical difference between the two groups in average abdominal pain relieved days, days of hospital stay and hospital charge as well as mortality.

Tetramethylpyrazine

Tetramethylpyrazine (TMP), an amide alkaloid monomer with typical feature of "calcium channel blocker" isolated from the rhizome of Ligusticum walliichi can potently dilate blood vessel, improve microcirculation, lower blood viscosity, improve blood rheology, and increase blood flow in microcirculation of viscera. It can indirectly dilate blood vessel by inhibiting TXA_2 synthesis, promoting generation of PGI_2, modulating TXA_2/PGI_2 imbalance, and increasing stability of lysosome membrane. TMP can raise surface charge of red cell and platelet, lower platelet aggregation, enhance transforming capacity of red cell, relieve high coagulative state, lower blood viscosity, and thus improve blood rheology, change blood flow during blood stagnancy, accelerate blood flow, maintain openness of capillary vessel, increase total blood flow, prevent thrombosis and enhance hemolysis. In addition, it can also eliminate oxygen free radicals (Qian *et al*., 1993) to resist oxidation. Ninty-five cases of SAP patients were randomly divided into 2 groups, the 50 cases of the treatment group were given TMP injection 100 ml, intravenously, once daily and after 5 d of treatment 31 cases were cured, 14 cases effective, 5 cases ineffective, total effective rate 90.0%, and there was no marked difference between treatment group and control group (Chang *et al*., 2003).

Tetrandrine

Tetrandrine (Tet), a bisbenylisoquinoline alkaloid isolated from the dried root of Stephenia tetrandra S Moore, is a calcium antagonist, now also used as PAF antagonist. PAF plays an important role in the occurrence and progress of acute pancreatitis and its complications. The mechanism of Tet for treating SAP might be: reduce PAF release by inhibiting Ca^{2+} inflow or inner calcium outflow (Zhang, 1993), inhibit PLA_2, reduce PAF release and can reduce the activation of PLA by PAF (He, 1995). Tet can reduce peroxidation injury by inhibiting pancreatin activation, inhibit the calcium overload of pancreatic acinar cell, stop NF-κB activation and alleviate pancreatic inflammatory reaction by its calcium antagonist function. Twenty-six cases of SAP patients were randomly divided into 2 groups, the treatment group took Tet tablets or dissolved physiological saline orally, tube clamp 0.5 h, 2 tablets each time, thrice daily and one week for a treatment period (Jiang *et al*., 2000). After treatment, 12 cases in treatment group were cured, 1 dead, recovery rate 92.3%, which indicates better treatment effect than that of the control

group. The main complication occurrence rate and mortality were all obviously lower than those of the control group.

Breviscapine

Breviscapine (Bre) also named scutellarein is ethanol extract water solution of the herb Erigeron breviscapus (ASTERACEAE). Its main ingredients are total flavone, Bre A and B. Bre can improve blood circulation, lower vascular resistance, inhibit intravascular coagulation and promote fibrolysis. Therefore, it can improve pancreatic microcirculation, lower blood viscosity, improve local blood supply of pancreas, correct ischemia and prevent necrosis. The total flavone can potently improve microcirculation, activate blood and eliminate stagnancy. It can relax blood vessel smooth muscle, dilate arteriole, especially sphincter before and behind capillary vessel (Xu, 2001). Bre B can lower red cell accumulation, inhibit platelet aggregation and raise TXB_2, TXB_2/6-keto-$PGF_1\alpha$ ratio, and also restore 6-keto-$PGF_1\alpha$ level after ischemia, inhibit intravascular coagulation, promote fibrinolysis and thus lower blood viscosity (Chen, 1998). In addition, Bre can enhance macrophage capacity and immune system, eliminate harmful oxygen free radicals, prevent and treat serious pathological and physiological reactions induced by calcium overload, and prevent neuron injury due to ischemia reperfusion. Sixty cases of acute pancreatitis patients were randomly divided into 2 groups (4 cases of SAP in treatment group, 5 in control group) (Yu *et al*., 2000). The treatment group was given Bre injection, and after completion of treatment period, 28 cases were cured, 2 cases were effective, total effective rate 100%, average days for cure 6.28 d, and all indexes for sign disappearance were better than those of the control group.

Sodium β-aescin

Sodium β-aescin, an extract from Aesculus hippocastanum (Hippocastanaceae), mainly plays roles in anti-effusion by influencing the metabolism of prostaglandin and increasing $PGF_2\alpha$ secretion and in anti-inflammation by increasing the secretion of cortisol compound. It can dilate arteriole, slowly and persistently contract veinule, improve the blood stagnancy of pancreatic microcirculation, accelerate microcirculation, eliminate inflammatory mediators and promote lymphatic return in order to reduce the inflammatory effusion of pancreas and eliminate pancreatic edema. It also can stabilize unit membrane, further reduce the injury of lysosome and mitochondria, restore the motor function of intestine, reduce intestinal bacterial translocation and eliminate intestinal infection. Fifty cases of acute pancreatitis patients were randomly divided into 2 groups (17 male patients and 33 female patients, age from 25 to 80, average age 42.5). The 24 patients in control group were only given conventional therapy while the 26 patients in treatment group were given sodium β-aescin plus conventional therapy. The result shows that after being treated by sodium β-aescin, the time required by acute pancreatitis patients to dispel abdominal pain, abdominal tenderness, restore normal intestinal functions and hemodiastase was markedly shorter than that of the control group (P<0.01) (Fu *et al*., 2003).

CONCLUSION

The conservative treatment of SAP by TCM monomers is quite significant. Markedly different from Western medicine such as somatostatin, TCM monomers not only act on pancreas, stomach and intestines, but also have marked treatment effects on other viscera injuries due to systemic inflammatory response accompanying pancreatitis and block pathological progress of SAP in a way. Its functions are more extensive than those of somatostatin and mutually supplementary. Therefore, the application of TCM monomers for treating SAP has significant clinical value and broad development prospect. We believe by further experimental study and clinical application that TCM monomer can become a promising preparation for clinical treatment of SAP.

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