

Emodin in Severe Acute Pancreatitis Treatment

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Abstract

Severe acute pancreatitis accounts for 15% - 20% of acute pancreatitis and is a kind of serious systemic disease because it involves multiple organ damage and dysfunction. Emodin is the most important active ingredient of rhubarb and has been used for the treatment of severe acute pancreatitis. This review mainly summarizes the study progress of emodin in severe acute pancreatitis treatment.

Keywords

Severe Acute Pancreatitis, Multiple Organ Damage, Emodin, Rhubarb

1. Introduction

Acute pancreatitis is an acute inflammation that causes pancreatic enzymes to be activated in the pancreas, causing subsequent pancreatic digestion, edema, bleeding, and even necrosis, of which about 15% - 20% are severe acute pancreatitis [1]. Severe acute pancreatitis is a kind of serious systemic disease because it involves multiple organ damage and dysfunction and the damage to non-pancreatic organs is often far more severe than the pancreatic damage itself [2]. Severe acute pancreatitis is characterized by severe clinical manifestations, poor prognosis and high mortality. The treatment of severe acute pancreatitis includes surgery and non-surgical measure. At present, it is thought that better effects of treatment can be achieved by combining rhubarb extracts or compound rhubarb preparation to medical treatment, which can effectively relieve clinical symptoms, reduce complications and mortality [3]. In this paper, the effects and mechanisms of emodin, a major effective ingredient of rhubarb, in the treatment of severe acute pancreatitis is reviewed.

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2. Causes of Severe Acute Pancreatitis

The common causes of severe acute pancreatitis include biliary, alcoholic, idiopathic and hypertriglyceridemia. Most of them are biliary, followed by idiopathic in China and alcoholic in western developed countries [4].

2.1. Biliary

The most important cause of severe acute pancreatitis is biliary [5]. According to a report, between 1990 and 2005, 1976 cases of severe acute pancreatitis were admitted to 15 medical centers in China, and 58.7% of them were caused by biliary tract diseases [4]. 337 cases of severe acute pancreatitis admitted to Peking Union Medical College Hospital were mainly biliary source as well [4]. Even in patients with idiopathic severe acute pancreatitis, the presence of bile duct stones should be taken into consideration. Approximately 20% - 50% of idiopathic severe acute pancreatitis is caused by biliary stones, with a maximum up to 60% - 80% [6]. The clinical examination of biliary microlithiasis is difficult, and it is easy to be misdiagnosed as idiopathic pancreatitis [7].

2.2. Idiopathic

If clinical, imaging, biochemical and other examinations could not find specific causes for severe acute pancreatitis, it should be considered as idiopathic [8]. Of the 1976 cases of severe acute pancreatitis admitted to the 15 medical centers in China between 1990 and 2005, 25.2% were idiopathic [4]. 19.8% of the 337 patients with severe acute pancreatitis in Peking Union Medical College Hospital were idiopathic [4]. With the development of research and the progress of detection technology, the causes of some of idiopathic severe acute pancreatitis can be identified, such as small stone disease, Audi sphincter dysfunction and others [9]. Reports from some other countries showed that idiopathic severe acute pancreatitis accounts for 20% of all severe acute pancreatitis cases.

2.3. Alcoholic

In western developed countries, alcoholism is the major cause of severe acute pancreatitis [10]. The proportion of alcoholic acute pancreatitis in China is lower than that in other countries, but there is a tendency to increase in recent years. Alcoholic acute pancreatitis is more common in young males. Although occasionally one-time heavy drinking can cause alcoholic severe acute pancreatitis, the vast majority of alcoholic patients with severe acute pancreatitis have a long history of large amount drinking, drinking more than 100 ml each day, lasting for more than 5 years [11] [12] [13]. Severe acute pancreatitis occurs in only 5% - 10% of alcoholics, suggesting genetic factors playing an important role.

2.4. Hypertriglyceridemia

Hypertriglyceridemia is one of the most important causes of severe acute pancreatitis, whereas hypercholesterolemia alone does not cause severe acute pan-

creatitis [14]. Due to the improvement of people's living standard and dietary structure, hypertriglyceridemia has become a common cause of severe acute pancreatitis in many areas [15]. Many years of research in Peking Union Medical College Hospital and Guangdong and Fujian showed that the incidence of hypertriglyceridemia-caused severe acute pancreatitis is on the rise. The causes of primary hypertriglyceridemia include type I, type IV and type V familial hypertriglyceridemia and the diagnosis of hypertriglyceridemia-caused severe acute pancreatitis depends mainly on clinical manifestations combined with hypertriglyceridemia. There is no significant association between the level of blood triacylglycerol and the severity of severe acute pancreatitis. Control of blood triacylglycerol levels can prevent the recurrence of acute pancreatitis [16].

3. The Pathophysiological Mechanism of Severe Acute Pancreatitis

The pathophysiology of severe acute pancreatitis is a complex and multifactorial process that has not yet been fully understood. Trypsin digestion and inflammatory mediators are widely accepted two basic theories. In recent years, the theories of oxidative stress and intestinal bacterial translocation have also attracted attention [4].

3.1. Trypsin Self-Digestion Theory

Trypsin self-digestion theory in twentieth Century was put forward in the 20th century. The doctrine deems that abnormal activation of pancreatic enzymes from proteolytic cleavage of trypsinogen in acinar cells leads to pancreatic auto-digestion, which happens in the early stage of acute pancreatitis, and eventually results in severe acute pancreatitis [17]. Bile reflux, duodenal reflux, obstruction of the pancreatic duct and the alcohol effect on pancreatic acinar and Audi sphincter causes ectopic activation of trypsinogen in the pancreas, the activation of trypsin, in turn, can activate other protease, leading to pancreatic chain digestive. The activation of trypsin in addition to destroying the pancreas itself resulting in destruction of pancreatic pancreatic hemorrhage and tissue necrosis, but also causes damage to surrounding tissue and distant organs through the circulatory system with damaged vascular endothelial and venous reflux [18] [19].

3.2. Inflammatory Mediator Release Theory

Severe acute pancreatitis is associated with excessive generation of inflammatory mediators and the end result is local and systemic inflammatory response [20]. The inflammatory mediators associated with severe acute pancreatitis include interleukin (IL), tumor necrosis factor (TNF), nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), and platelet activating factor, which are correlated and exert mutual influence [21]. IL-1 is produced in the early stage of inflammation and plays an important role in the early phase of se-

vere acute pancreatitis. The pro-inflammatory cytokines IL-6 and IL-8 are also elevated and correlated with the severity of severe acute pancreatitis. However, the level of anti-inflammatory cytokines such as IL-2 and IL-10 decreases significantly, resulting in the imbalance of anti-inflammatory and pro-inflammatory cytokines. TNF- α is an inflammatory mediator, but can also serve as a chemotactic factor to induce the aggregation of other inflammatory mediators. The promoter of TNF-, IL-1, IL-6 and IL-8, and some other inflammatory mediator possesses binding site for NF- κ B and their expression subject to the regulation of NF- κ B; inhibition of NF- κ B can reduce the expression of these pro-inflammatory mediators [22]. In severe acute pancreatitis, the expression or activation of various inflammatory mediators takes a cascade reaction; the diffusion of inflammatory mediators leads to systemic inflammatory syndrome and multiple organ failure.

3.3. Oxidative Stress Theory

In severe acute pancreatitis, hyperactivation of white blood cells in the pancreas leads to respiratory outburst, producing a large amount of oxygen free radicals. Oxygen free radicals and their derived active substances can cause severe damage to pancreatic tissue, in which hydrogen peroxide and superoxide play an important role in cell injury. Oxygen free radicals and their derivatives can also cause microvascular endothelial cell damage and leukocyte adhesion, increase capillary permeability, and cause microvascular spasm and pancreatic microcirculation disorders. Excessive oxygen free radicals destroy acinar cells and activate the pancreatic enzymes inside and outside the cells, leading to a vicious cycle of pancreatic injury in severe acute pancreatitis [23] [24].

3.4. Intestinal Bacteria Translocation Theory

Intestinal flora under normal conditions will not break through the intestinal mucosal barrier and translocate to the intestinal tissue. In severe acute pancreatitis, decreased intestinal blood perfusion, intestinal mucosal ischemia-reperfusion, increased vascular permeability, dysfunction of intestinal motility, intestinal mucosal barrier damage, compromised local and systemic immunity, and intestinal bacterial overgrowth work together to enable the intestinal flora (and endotoxin as well) to move directly into the peritoneal cavity or indirectly through the blood and lymph circulation or through the bile duct and the pancreatic duct retrograde translocation, which stimulates the activated macrophages to secrete excessive inflammatory mediators, conflicting a secondary attack on the pancreas and all the other organs of the body [25] [26].

4. The Mechanism of Emodin in the Treatment of Severe Acute Pancreatitis

Rhubarb (*Rheum rhabarbarum*) is a species of plant in the family Polygonaceae. It is an herbaceous perennial plant. In China, the plant is mainly used as a medi-

cinal herb, and the medicinal part of rhubarb is the dried root and rhizome. According to traditional Chinese medicine, Rhubarb is bitter and cold, and it goes to the stomach, liver and colon channels. Some 200 compounds have been isolated from rhubarb, which are divided into six skeleton structures, including Anthraquinone, anthrone, pyranone, acylglycosides, stilbene glucosides, and flavanes [27]. Among them, emodin (Figure 1) of the anthraquinone (1,3,8-trihydroxy-6-methyl-9,10-anthraquinone) is the most important active ingredient for the treatment of severe acute pancreatitis [28]. Emodin exerts its effect in the treatment of severe acute pancreatitis through the following mechanisms [29].

4.1. Inhibiting the Production and Release of Inflammatory Mediators

A large number of studies have demonstrated that Emodin can reduce the production and release of TNF- α , IL-6, IL-1 β and other inflammatory factors in serum and pancreatic tissues during acute pancreatitis. [30]. Researches showed that the mechanism of emodin to inhibit the inflammatory response of severe acute pancreatitis may be related to the reduction of DNA binding activity of NF- κ B in pancreatic tissue [31] [32]. Emodin also up-regulate the expression of intercellular adhesion molecule 3 (ICAM-3) in rat peritoneal macrophages, enhance phagocytosis of the peritoneal macrophages, and thus reduce the inflammatory reaction in severe acute pancreatitis. Using inverse bile duct injection of sodium taurocholate to induce SD rat model of severe acute pancreatitis followed by emodin intervention of severe acute pancreatitis in the rats, researchers found that emodin can significantly reduce endoplasmic reticulum stress of pancreatic acinar cells in the severe acute pancreatitis rats, can reduce the expression of endoplasmic reticulum stress sensor proteins BIP and IRE1 α in pancreas and the expression of their downstream signaling molecules TRAF2 and ASK1, and can inhibit phosphorylation of c-Jun N-terminal kinase (JNK) and p38MAPK in the inflammation signal pathway, thereby inhibiting the release of the inflammation factor TNF- α and IL-6 [33]. Studies also found that in some of the experimental rat model of severe acute pancreatitis induced by the inverse bile duct injection of sodium taurocholate, emodin reduced the release of serum and pancreas inflammatory cytokines in severe acute pancreatitis rat, which may be related to decreased expression of closed protein-5, stromal derived factor-1, and Toll like receptor-4 in pancreatic tissue [34] [35].

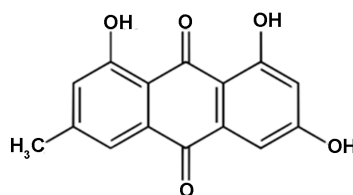


Figure 1. Skeletal formula of emodin.

4.2. Inhibiting the Release of Pancreatic Enzymes in Severe Acute Pancreatitis

The severity of severe acute pancreatitis is positively correlated with pancreatic enzyme levels, and serum amylase and lipase levels can be up to 5 to 10 times the normal value. The release of pancreatic enzymes not only have direct damage to tissues and organs, but produce cascade inflammation reactions and cause multiple organ and system damage as well by activating a variety of immune cells to release a large number of inflammatory mediators via certain signaling pathways. The main function of pancreatic acinar cells is to secrete a variety of digestive enzymes, including trypsin, pancreatic lipase, and pancreatic amylase. Studies found that emodin can strongly inhibit the release of pancreatic enzyme in severe acute pancreatitis [36]. Wu *et al.* used cerulein combined with lipid polysaccharide to stimulate in vitro the rat pancreatic acinar cell line AR42J to mimic the in vitro model of severe acute pancreatitis and that was followed with emodin intervention. The results of the study showed that compared with model group, AR42J cells in the emodin intervention group expressed and secreted significantly less amylase; this may be due to emodin can reduce pancreatic acinar cell's calcium overload, reduce the endoplasmic reticulum stress [37].

4.3. Inducing Pancreatic Acinar Cell Apoptosis

Kaiser *et al.* first found that the severity of acute pancreatitis was negatively correlated with the degree of apoptosis of pancreatic cells and suggested that apoptosis may be a favorable response of the pancreas to injury [38]. Apoptosis is the programmed and orderly death of cells without releasing cell contents. During apoptosis, apoptotic cells or apoptotic bodies are engulfed by surrounding cells or macrophages, and the contents of the cells are not released to the surrounding environment. By contrast, when cells undergo necrosis, they release their contents to the surrounding environment [39] [40]. Studies have shown that inducing pancreatic acinar cells to undergo apoptosis in advance can prevent pancreatic acinar cell from necrosis and avoid cell contents release including the release of pancreatic enzymes and thus reduce the severity of severe acute pancreatitis. Emodin was injected intraperitoneally to severe acute pancreatitis model rats to intervene for 12 hours, and apoptosis of pancreatic acinar cells in each group was detected by TUNEL assay (Terminal deoxynucleotidyl transferase mediated dUTP Nick End Labeling assay). The results showed that compared with the severe acute pancreatitis group without emodin intervention, the apoptosis of pancreatic acinar cells in the emodin intervention group increased significantly, suggesting that one of the mechanisms for emodin to inhibit pancreatic enzyme secretion in severe acute pancreatitis is through promoting apoptosis of acinar cells [41]. By using reverse transcriptase polymerase chain reaction (RT-PCR) technique to detect the expression of the apoptosis promoting gene Bax mRNA before and after emodin treatment of acute pancreatitis, it was found that the expression of Bax mRNA in emodin group was significantly higher than the

model group, indicating that emodin may promote apoptosis through inducing Bax mRNA expression [42].

4.4. Protecting Intestinal Mucosa and Muscle Cells

Intestinal mucosal barrier includes mechanical barrier, biological barrier, immune barrier and chemical barrier. It has the function of maintaining internal environment stability and regulating intestinal flora and preventing intestinal bacterial translocation. Current researches suggest that the main reason for the high fatality rate of severe acute pancreatitis is the high permeability of the intestinal mucosal barrier which leads to translocation of enteric bacteria and endotoxin, resulting in peripancreatic and systemic infection secondary to severe acute pancreatitis [43]. The injection of different doses of emodin into the jejunum can significantly reduce the level of serum inflammatory factors in severe acute pancreatitis rats [44]. Studies showed that emodin can inhibit excessive apoptosis of intestinal mucosa cells, increase serum leptin levels, and maintain the integrity of the intestinal mucosal barrier, which can inhibit bacterial endotoxin translocation in severe acute pancreatitis [45] [46]. In a research [29], severe acute pancreatitis rat model was established by inverse bile duct injection of sodium taurocholate, which was followed with emodin intervention; the study found that emodin could significantly decrease cytochrome C positive expression and apoptosis of rat small intestine smooth muscle cells, and meanwhile mitochondrial membrane potential of the smooth muscle cells in the severe acute pancreatitis group was increased significantly, suggesting that emodin may inhibit the apoptosis of intestinal smooth muscle cells by reversing the ultrastructural changes of the cells, and thus play a protective effect on intestinal dynamics.

4.5. Protect the Heart, Lung, Liver, Kidney and Other Organs

Severe acute pancreatitis is a serious disease involving multiple organs. About 90.9% of the patients suffer from multiple organ failure. About 90.9% of deaths were complicated with respiratory failure, 86.4% with cardiovascular failure, and 50% with renal failure. Therefore, the treatment effect of other organ dysfunction caused by severe acute pancreatitis will directly affect the prognosis of the disease and the survival rate of the patients. Studies showed that emodin can reduce myocardial injury in rat model of severe acute pancreatitis; the protective effects on myocardium may be through inhibiting the production of inflammatory mediators and activating the ATP sensitive K^+ channels on mitochondrial membrane so as to counteract apoptosis [47]. Respiratory distress syndrome is one of the most common complications of severe acute pancreatitis and is also the leading cause of death in severe acute pancreatitis. It was found that emodin could prevent acute pulmonary injury from developing into respiratory distress syndrome [48]. In cases of severe acute pancreatitis complicated with hepatic function damage, transaminase and bilirubin are elevated. A study found that severe

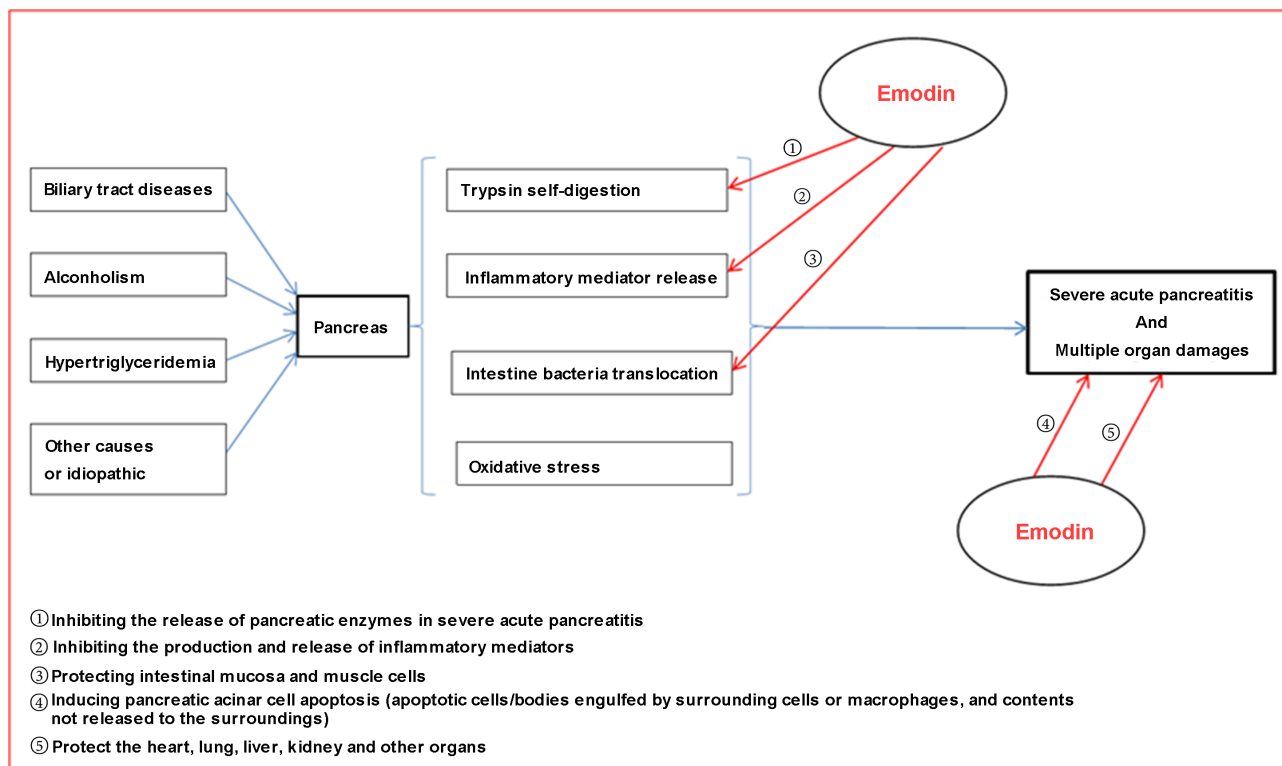


Figure 2. Summary of the etiology and mechanism of severe acute pancreatitis and roles of emodin in the treatment of severe acute pancreatitis.

acute pancreatitis model rats treated with emodin had lower transaminase and bilirubin levels than the non-treated group, indicating that emodin had protective effect on the liver [49]. Emodin also has a good effect on the protection of renal function. Clinical studies have found that the kidney function of patients with routine plus emodin treatment is much better than that of the routine only treatment group [50].

5. Conclusion

In recent years, with the progress of the understanding of severe acute pancreatitis, more attention has been paid to the combination of traditional Chinese medicine and western medicine in treating the disease. Application of emodin to the treatment of severe acute pancreatitis has made certain progress both in experimental study and clinical practice. Emodin in treatment of severe acute pancreatitis has the characteristics of multiple way and multiple targets; it acts not only on the pancreas and the gastrointestinal tract but also on other organs and has significant therapeutic effects on systemic inflammatory reaction accompanying severe acute pancreatitis; it can to some extent block the pathological progress of severe acute pancreatitis (Figure 2). But at present, the research of emodin's action mechanism pertaining to signaling pathways is insufficient; the sample of clinical investigation is generally small; and there has not yet been a consensus conclusion about the optimum dosage of emodin and the best medi-

cation time point; all these need to be further studied.

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