Archives of Pharmaceutical Sciences Ain Shams University 2022; Vol. 6(2):292-308

OPEN ACCESS

Pharmacology and Toxicology

Review Article

Mechanistic insights into the pathogenesis and management of acute pancreatitis

Naglaa Gamal Ahmed[a], Mariane G. Tadros[b], Haidy E. Michel[b*]

[a]*Egyptian Drug Authority (EDA), Giza, Egypt*
[b]*Department of Pharmacology and Toxicology, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt*

Abstract

Acute pancreatitis (AP) is an inflammatory disorder of the pancreas; its incidence rate is increasing worldwide; it is around 34 cases per 100,000 persons /year. It may range from mild to severe cases and may be associated with morbidity and mortality mainly due to multiple organ dysfunction syndromes (MODS). Till now, there is no specific therapy for the disease and the treatment of AP is mainly supportive. Moreover, the underlying mechanisms included in its pathogenesis are not fully clear. However, it may include oxidative stress and inflammatory response, including critical mediators, such as interleukin-1β (IL-1β), tumor necrosis factor- α (TNF-α), toll-like receptor-4 (TLR-4), nuclear factor-kappa B (NF-κB), and high-mobility group box protein1 (HMGB1). Thus, there is a pressing need for continuous search in this era to clarify different pathogenesis and the development of new treatment options for AP, also understanding the disease. While research on the human pancreas remains challenging, animal models of AP may help to elucidate the disease pathophysiology & to discover new target options for the development of new therapies. This review aims to revise several aspects related to AP diagnosis and management and to summarize different animal models of AP.

Keywords: *acute pancreatitis; inflammation; autophagy; animal models; new treatments.*

***Correspondence** | Haidy E. Michel; Department of Pharmacology and Toxicology, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt. Email: heidieffat@pharma.asu.edu.eg

Citation | Ahmed NG, Tadros MG, Michel H E, 2022. Mechanistic insights into the pathogenesis and management of acute pancreatitis. Arch Pharm Sci ASU 6(2): 292-308

DOI: 10.21608/aps.2023.179734.1104

Print ISSN: 2356-8380. **Online ISSN**: 2356-8399.

Received 17 January 2023. **Accepted** 11 March 2023.

Published by: Ain Shams University, Faculty of Pharmacy

1. Introduction

Acute pancreatitis (AP) is an inflammatory disorder of the pancreas; it has substantial morbidity and mortality **[1]**. AP may range from mild self-limiting to severe cases, which are frequently associated with complications and a high mortality rate **[2, 3]**. Most cases are mild but about 20% develop multiple organ dysfunction syndrome (MODS) which is the main cause of high mortality **[4]**. AP is considered an essential cause of hospitalization due to gastrointestinal disease **[5]**. Previous data show that the AP mortality rate ranges from 1% to 5% which was reduced due to improvement in diagnosis & care while the hospitalization rate & cost increased **[6]**, but recent data showed that Mortality for AP is approximately 1% overall; however, in case of AP associated with organ failure, mortality may be as high as 30%–40%.5 **[7]**. There are continuous advances in the supportive management of AP, but to date, no specific effective drug is available to treat or prevent AP. Nevertheless, important advances for the

identification of new targets for potential drug development are ongoing, for instance: studying calcium signaling pathways in AP resulted in the discovery of calcium release-activated channels and mitochondrial permeability transition pores that could be promising targets **[1]**. However, the overall development of new therapies with new potential targets is still urgently needed.

2. Prevalence & etiology

AP has an increasing incidence rate worldwide, approximately 34 cases per 100,000 persons/year **[1]**. This may be due to the increase in gallstone disease or may be due to the increase in routine testing of pancreatic enzymes in patients having abdominal pain at admission to the emergency department **[8]**. It is important to identify the etiology of acute pancreatitis for early and effective management of AP and prevention of recurrence **[8]**. Many studies revealed that gallstones are the most common cause of AP, followed by alcohol consumption **[9]**. Those causes comprise around 75%–80% of the cases **[1, 10]**. Gallstone AP was found to be more common in female subjects while alcohol pancreatitis was more common amongst men and idiopathic pancreatitis was similar in both sexes **[8]**. There are other uncommon causes for AP, such as hypercalcemia, drugs, and tumors as shown in **Table 1**. Furthermore, the cause of AP is unknown in nearly 10% of the cases **[8]**.

Table 1. Various etiologies of acute pancreatitis [11]

Common causes	Uncommon causes	Rare causes
• Gallstones	• Pancreas divisum	• Infective: Coxsackie virus, mumps, HIV, parasitic. Ascariasis
• Alcohol	• Periampullary cancer	
• Idiopathic Hyperlipidemia	• Cancer of the pancreas	
• Hypercalcemia	• Periampullary diverticulum	• Autoimmune: systemic lupus erythematosus, Sjogren‟s syndrome
• Sphincter of Oddi dysfunction	• Vasculitis	
• Drugs and toxins		
• Post-endoscopic retrograde		• α-1 antitrypsin deficiency
• cholangiopancreatography		
• Traumatic Postoperative		

3. Pathogenesis

The pathogenesis of AP is mainly due to the inappropriate activation of trypsinogen to trypsin which autodigests pancreatic tissues leading to necrosis of acinar cells and pancreatic islets **[8]**. The actual mechanisms of acute pancreatitis are not fully clarified but there are many hypotheses. Despite continuous investigations, the pathogenesis of AP is not completely unraveled **[12]**; however, it may include oxidative stress **[13, 14]** and inflammatory response **[15]**.

Several theories explain how stone causes AP. One theory assumes that a stone may create a channel behind it that allows bile reflux and injure the gland to cause pancreatitis. Another theory assumes that the stone passing reduces the efficiency of the sphincter and causes the reflux of duodenal juice with pancreatic enzymes that can reflux through the inefficient sphincter into the pancreatic ductal system. Another theory assumes that the stone passage obstruction may cause inflammation and edema eventually leading to continuous secretion into the pancreatic ductal system **[16]**. AP caused by gallstones can be explained as the gallstone may lodge the sphincter of Oddi **[17]**.

The resulting duct obstruction may lead to an increase in the pressure in the pancreatic duct that may lead to acinar cell damage and digestive enzyme activation **[8]**. The second most common cause of AP is alcohol consumption **[9]**. The main mechanism of pancreatitis caused by alcohol consumption is unknown but it can be explained by a combination of genetic and environmental factors **[8]**. Many processes were assumed to be involved in the pathogenesis of AP, such as early trypsinogen activation, impaired autophagy, mitochondrial dysfunction, and endoplasmic reticulum stress **[1]**. Oxygen-derived free radicals and many cytokines (e.g.TNF-α, interleukin [IL]-1, IL-6, IL-8) also have important roles in AP **[10]**. In **the** cerulein-induced AP model, it was revealed that there were very high levels of pro-inflammatory cytokines, TNF-α, IL-1β, and IL-6 in the serum. They were released from acinar cells as a result of damage to the pancreas **[18, 19]**.

The changes occurred in the pancreatic gland lead to the release of active pancreatic enzymes that stimulate an inflammatory response **[8]**.

3.1. Mechanisms could be involved in AP pathogenesis

3.1.1. Inflammation

Inflammatory mediators play an important role in AP and MODS which is the primary cause of death. Many studies evaluate & confirm the role of inflammatory mediators in AP such as TNF-α, IL-1β, IL-6, IL-8, Platelet-activating factor (PAF), IL-10, The complement activation product (C5a), Intercellular adhesion molecule-1 (ICAM-1) **[20-23]**.

The local inflammatory response could result from Acinar cell damage which could also lead to a systemic inflammatory response. Systemic inflammatory response determines the severity of an AP & could cause Systemic leukocyte release that can lead to distant organ damage and MODS **[20, 24, 25]**.

As shown in **[26]** IL-6 and IL-8 levels were elevated in the case of renal, respiratory, and circulatory failure resulting from AP, as was the case for multi-organ failure, while TNF-α was elevated in all types of organ failures, except for intestinal failure. TNF-α elevation cause the release of other cytokines **[27]**.

Toll-like receptor-4 (TLR-4) has a vital role in the innate immune response **[28]** and plays an important role in the pathogenesis of AP **[29, 30]**. It activates nuclear factor-kappa B (NF-κB). NF-κB is a transcription factor that is important for inflammatory signaling **[31]**. Activation of NF-κB occurs through phosphorylation of its inhibitor protein kappa B (IκB) that is bound to it by IκB kinase (IKK) and rapidly degraded to be active **[32]**. Activation of NF-κB stimulates the release of other cytokines to initiate the inflammatory response such as (TNF)-α, IL-1β, other chemokines such as macrophage inflammatory protein (MIP)-1, IL-8, and monocyte chemoattractant protein (MCP)-1, PAF and adhesion molecules **[33]**. It was shown that the NF-κB level increased in AP **[21]**, while the reduction in its level was associated with

improvement in AP **[33, 34]**.

High-mobility group box protein1 (HMGB1) is a nuclear protein secreted from necrotic cells or by activated macrophages or monocytes, can start an inflammatory signaling cascade by binding to the receptor for advanced glycosylation end product (RAGE) and Toll-like receptors 2 (TLR2) and TLR4 **[35]** which is crucial in the pathogenesis of AP. Treatment that causes suppression of HMGB1 to reduce the severity of AP **[35, 36]**.

3.1.2. Oxidative stress

Oxidative stress plays an important role in the initiation of AP. Reactive oxygen species (ROS) are generated at an early stage of the disease **[37]**. Levels of the superoxide radical &lipid peroxides increased while ascorbic acid levels decreased in the early phase of AP. Also, the relation between disease severity & presence of oxidative stress was confirmed **[38]**. Levels of malondialdehyde (MDA) also increased in AP **[34]** & levels of glutathione were reduced and depleted during the development of AP **[39]**. Antioxidant use in cerulein-induced pancreatitis reduced pancreatic tissue damage, and also hampered the extrapancreatic complications, thus improving the outcome of the disease **[37]**. It was found in a study that used antioxidant in an AP animal model that acinar cell injury and edema is reduced after treatment **[39]**.

3.1.3. Autophagy

A process in which damaged proteins and organelles are transferred to lysosomes for digestion and degradation. Normally autophagy prevents cancer development. But if cancer already exists autophagy usually supports the cancer cell growth & survival **[40]**. Autophagy can be stimulated in other diseases as autophagy is stimulated by multiple factors, like nutrient deprivation and stress, as a cell survival mechanism. However, deregulation of the autophagic process can lead to harmful effects in AP **[41]**.

LC3 is autophagic activity marker **[42, 43]**, and is significantly increased in AP **[44] to** activate autophagy in AP rat models **[41]**.

HMGB1 regulates autophagy **[45]**, which was demonstrated to be activated in AP **[41]**, as evidenced by the elevated levels of autophagic genes such as Beclin1 and microtubule-associated protein 1A/1B-light chain 3 (LC3-II) **[41, 43]**. LC3& berlin-1 are autophagy proteins, their levels were elevated in AP while reduction of their levels is associated with improvement in AP **[46]**. Beclin1 is an autophagic gene that induces autophagy through the formation of a complex with Atg14, Vps34/ class 3 phosphatidylinositol 3-kinase (PI3k), and Vps15 **[47]**.after stimulation by HMGB1 **[48]**.

4. Pathophysiology

AP can cause MODS including progressive renal and liver failure **[49]** which is considered the primary cause of morbidity and mortality **[50, 51]**.

Pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α,) play a significant role in the pathogenesis of AP and systemic complications **[52]**. AP pathophysiology can be explained as stages. Firstly, activation of pancreatic trypsin in acinar cells and activation of many cytokines & inflammatory mediators occurs. Activated trypsin activates other enzymes including phospholipase and elastase. The active enzymes and cytokines then digest cellular membranes and cause edema, proteolysis, interstitial hemorrhage, vascular damage, and cell necrosis **[53]**. During AP progression, Cytokines continue to be released from the necrotic acinar cells & the immune cells to cause more pancreatic inflammation, which leads to the systemic inflammatory response. Moreover, it can cause distant organ damage including acute respiratory distress syndrome, or

MODS **[53, 54]**. MODS are associated with high levels of cytokine and C-reactive protein in the circulation. The endothelial barrier damage in various organs may be involved in the pathophysiology of MODS resulting from AP. It is also accompanied by increased permeability which allows the transfer of blood constituents to various tissues, including the pancreas, lungs, kidneys, colon, spleen, and intestine **[55]**.

4.1. AP severity

Pancreatitis severity can be categorized according to the revised Atlanta classification, as mild, moderate, or severe. Mild AP is characterized by the absence of organ failure, local complications, or systemic complications. Moderately severe AP is characterized by the presence of transient organ failure (<2 days) and local complications, while severe acute pancreatitis is characterized by the presence of persistent organ failure (>2 days) **[56]**. **Table 2** shows the difference between the revised Atlanta classification and determinant-based classifications of AP.

Table 2. Difference between revised Atlanta classification & determinant-based classifications of acute pancreatitis [1]

Classification	Mild	Moderately severe	Severe	Critical
Revised Atlanta classification	No organ failure, local complications, or exacerbation of the comorbid condition	Transient organ failure (<48 h), local complications, and/or exacerbation of the comorbid condition	Persistent organ failure	NA
Determinant-based classification	No organ failure and no (peri)pancreatic necrosis	Sterile (peri) pancreatic necrosis and/or transient organ failure (<48 h)	Persistent organ failure (>48 h) or infected (peri)pancreatic necrosis	Persistent organ failure (>48 h) and infected (peri)pancreatic necrosis

4.2. Animal models

Conduction of studies on AP on the human pancreas is very difficult for many reasons, such as disease heterogenicity and limited samples, so it is more practical to conduct studies on animals **[57]**. Animal models were used in recent years mostly to help in clarifying the underlying mechanisms of AP and/or examine therapies. Pathophysiological mechanisms of interest as well as the disease phase of interest are the determinant factors of the model type. The most commonly used animals are rodents (rats and mice) due to many reasons, such as that they are relatively inexpensive, easy to handle, and accessible. However, one of the drawbacks of

animal models is that late complications are not usually studied in acute cases. Also, the differences between human and animal pancreas should be recognized. Several animal models of acute pancreatitis are available. The most common models are briefly discussed below.

4.3. Cerulein

Exocrine pancreas damage can be induced by neural stimulation. Cholecystokinin stimulates the pancreas and also does its analog, cerulein **[58]**. Excessive doses of cerulein at repeated intervals result in AP **[59]**, which is characterized by cytoplasmic vacuolization, acinar cell necrosis, edema formation, and inflammatory response **[1]**. Cerulein can be administered subcutaneously, or intravenously. Acute pancreatitis caused by cerulein is mild **[15]**, rapidly resolves, and is not accompanied by any mortality. Cerulein-induced pancreatitis models are characterized by low cost and high reproducibility **[57, 60]**.

4.4. Basic Amino Acids

Intraperitoneal (i.p.) administration of many doses of certain amino acids causes AP in mice or rats, such as L-arginine **[61]**, L-lysine **[62]**, L-ornithine **[63]**, and L-histidine **[64]**.

4.4.1. L-arginine

L-arginine-induced AP is currently the most commonly used amino acid-induced AP model in rats and mice. L-arginine was used to induce AP for the first time in 1984 as a single i.p. injection at 5 g/kg and led to necrosis of tissues in the rat pancreas, without affecting islets of Langerhans and other organs **[65]**. After that, L-arginine was used with different doses & gave reproducible results **[66]**, such as two doses of 4 g/kg each, at 1 h apart **[67]**. When higher doses (7.5 g/kg) of L-arginine were used, it caused a lethal effect on animals, while the lower dose of 2.5 g/kg caused mild injury in the pancreas. Many studies used either single or double injections of L-arginine at different doses to induce AP in rats or mice **[68]**. The L-arginine model is characterized by its reproducibility and suitability for the early and late phases of acute pancreatitis testing. However, it has a disadvantage in that its long-term administration induces chronic pancreatitis **[69]**. The mechanism by which L-arginine causes AP is not well-known but it was thought that inflammatory mediators **[65]** or reactive oxygen species **[70]** could play an important role in this process. The increase in amylase and lipase levels occurring in L-arginine induced model was further supported by histopathological changes, which showed accumulation of fluid around acini, vacuolization, and marked necrosis of acinar cells which was significantly greater than that observed in cerulein-induced pancreatitis.

4.1.2. L-lysine

L-lysine is an amino acid used with different doses to induce AP. It was used at a dose of 2 g/kg causing mitochondrial damage that was followed by the activation of NF-κB & trypsinogen **[62]**. Another study used L-lysine at a dose (400 mg/100 g body weight) and showed similar results **[71]**.

4.1.3. L-ornithine

L-ornithine was used for induction of AP in rats by i.p. injection at a dose of 3 g/kg. Examination of the pancreatic tissue showed that L-ornithine use leads to necrosis of acinar cells and massive interstitial edema **[63, 72]**.

4.1.4. L-histidine

Histidine was used for induction of AP in rats by i.p. injection at 2 × 4 g/kg L-histidine free base. Examination of the pancreatic tissue showed that L-ornithine use leads to necrosis of acinar cells and massive interstitial edema **[73]**.

4.2. Taurocholate-induced model

In this model, pancreatitis was induced by sodium taurocholate infusion into the bile duct **[74]**. It was shown that the pancreatic injury caused by sodium taurocholate was more severe than that caused by cerulein. It causes a high mortality rate of up to 60% within the first 24 hours after administration **[75]**. Taurocholate-induced pancreatitis animal models are severe, and it was thought to most closely resemble clinical biliary pancreatitis, so they are used often **[5, 34, 75, 76]**. However, these models have some limitations, such as a high death rate and prolonged preparation time **[77]**.

4.3. Alcohol-induced model

Several animal studies used alcohol to induce AP to investigate the underlying pathophysiological mechanisms of alcohol-induced acute pancreatitis. Unfortunately, the administration of alcohol barely produces significant damage **[78, 79]** and requires being prior sensitized by other agents to allow significant pancreatic damage to occur **[80, 81]**. Ethanol can be administered intravenously or by oral route, and animals that can be used in this model include rats, cats, and dogs **[82]**.

4.4. Bile duct ligation

Ligation of the common bile duct results in leakage of bile back into the pancreatic duct with subsequent inflammation. This model has been used in larger animals, including possums **[15]**. This model clarified the importance of pancreatic duct obstruction as the central initiator of gallstone acute pancreatitis. However, this model has disadvantages, such as high intra-animal variability and the inability of opossums to be bred in the laboratory **[83, 84]**.

4.5. Diet-induced pancreatitis

A diet deficient in choline and supplemented with ethionine induces hemorrhagic pancreatitis resembling human disease **[15]**. It can be used for studying pathophysiology for AP and potential experimental treatment. It is a simple, cheap, non-invasive, and highly reproducible method. However, it can be only used in female mice, requires careful monitoring, and is associated with high mortality **[69]**.

4.5.1. Diagnosis

Diagnosis of AP depends on many criteria, like laboratory tests, imagining techniques, and physical examination **[85, 86]**. AP can be diagnosed when two of three conditions are met, two of them are abdominal pain & increase of serum amylase and/or lipase level at least three times the upper limit of normal level which is between 100-300 U/L for amylase and 50 - 160 U/l for lipase. The third condition is imaging techniques of the abdomen after 72 h from the symptoms start mainly by contrast-enhanced computed tomography to show findings like gland edema and peripancreatic fat stranding **[1]**. Imagining techniques include Magnetic Resonance Imaging **[86]**. There are some challenges to these criteria, for example in alcoholics and patients suffering from high levels of triglycerides, the amylase levels can be normal. Another challenge is that there are other cases in which the amylase and lipase levels are increased, like obstruction and abdominal aortic aneurysm in the case of amylase and acute intestinal pathologies, cholecystitis, peptic ulcer disease, and biliary obstruction in case of lipase **[1]**. The abdominal pain and elevated levels of pancreatic enzymes in the serum are very important in diagnosis **[8]**. Pancreatic enzyme assessment is a critical step used in the diagnosis with the preference for lipase over amylase **[85]** because it is slightly more specific and sensitive than amylase and has a longer half-life. Their levels rise to the peak early while and turn down over 3-4 days of the initial attack **[8]**. Quick diagnosis is extremely essential in the reduction

of the morbidity and mortality associated with AP **[52]**. In case of suspicion of a biliary etiology, a trans-abdominal ultrasound (T-A US) must be done first to demonstrate gallstones and any other pathological change .and if it appears normal with strong suspicious of biliary cause Magnetic resonance cholangiopancreatography or the endoscopic US should be performed to investigate the causes of duct obstruction **[8]**.

The most common symptom of AP is acute abdominal pain and tenderness in the upper abdomen which is commonly occurred in another abdominal diseases. Abdominal pain occurs in nearly 95% of the patients. The pain is usually acute & reaches maximum intensity rapidly and it is usually generalized to the upper abdomen **[8]**, but it could be more localized to the right upper quadrant, epigastric area, or, rarely, left upper quadrant **[87]**. Moreover, nausea and vomiting occur in the majority of the patients **[8]**. Fever also is an important sign in patients with acute pancreatitis. Most patients develop a fever at the start of the illness **[11]**.

While it is very important to early diagnose for better management, it is difficult to identify MODS cases early. Many predictors of MODS exist including pancreatic injury markers and inflammatory response markers & clinical features **[52]**.

4.5.2. Management of acute pancreatitis

Incompatibility between the rapid onset of the AP attacks and the slow rate of hospitalization makes the management of AP challenging. It is important to identify the risk factors early during the first 24 h after hospital admission **[88]**.

Management of AP mainly aims to the reduction of complications by focusing on preserving organ perfusion. Thus, management includes analgesics & antiemetic administration, oxygen administration, fluid restoration & continuous patient evaluation to detect any organ dysfunction or complication **[8, 89]**. Loss of a large volume of fluid increase the incidence rate of renal failure & associated mortality. To restore intravascular fluid volume rapidly the patient may administer fluids at a rate of 300 to 500 ml/h which may lead to electrolyte imbalance **[90]**. Balanced electrolyte solutions (9% saline or Ringer‟s lactate) should be given rapidly then frequent assessment of the patient‟s volume status should be done by assessing heart rate, blood pressure, and urine output **[11]**.

Control of pain is very important as patients with pain tend to have a high respiratory rate from hypoxic „drive‟, which can lead finally to the reduction of lung function. Furthermore, it can increase the risk of deep venous thrombosis. The therapy of choice, in this case, is Narcotic analgesics which are administered via an epidural catheter. As AP results in rapid loss of body weight, fat, and protein, so nutritional support is an essential step in patient care **[11]**. Early introduction of a solid, low-fat diet in patients with mild or moderately severe pancreatitis is supported by evidence & is preferable for those patients who can tolerate an oral diet **[91, 92]**. If patients with mild–moderate AP do not tolerate oral food within approximately 3–5 days, the enteral tube feeding should be used **[93]** (total parenteral nutrition) plays a role in seriously ill patients with acute pancreatitis Otherwise, patients with severe disease who are not expected to eat for a week or more should be considered for (preferably enteral) nutritional support at an early stage **[94]**. It is useful to use prophylactic antibiotics in severe acute pancreatitis as approximately 80 percent of deaths from AP result from infectious complications but should be of broad spectrum, and should be used for a short period (5–7 days) **[95]**. Moreover surgical, endoscopic, or radiologic drainage procedures may be required for patients with

infected necrosis **[96]**. Management of AP resulting from gallstone, endoscopic intervention, and endoscopic intervention is recommended for removal of the stone(s) which has success rates over 90% **[11]**. MODS that may result need close monitoring and may require management in the intensive care unit, accordingly as a minimum in this case peripheral venous access, a central venous line, and a urinary catheter are needed. Also, management of acute respiratory complications may require intubation and mechanical ventilation. Acute renal failure can occur & it will be diagnosed depending on the presence of one of the following: (i) increase in serum creatinine > 0.5 mg/dL (44 mmol/L) or 50% above baseline; (ii) reduction in the calculated creatinine clearance >50%; or (iii) a need for dialysis **[11]**. According to recent guidelines, there is no new update in the management of AP regarding fluid resuscitation, pain control, early oral feeding & local complications treatment, while the routine use of antibiotics; is not recommended **[97]**. The Korean guidelines recommendation regarding antibiotic use was aligned with other reviews about antibiotic use in AP cases [**98, 99]**.

To date, there is no specific therapy for AP but there were trials for developing potential pharmacologic therapies for the management of AP. Depending on mechanisms involved in AP pathogenesis like inflammation, oxidative stress & autophagy, different therapies were investigated. Glycyrrhizin was found to have antioxidant & anti-inflammatory effects in AP **[100]**, and improved pancreas lesions in the AP model **[101]**. A Chinese herbal formula called "Chaiqin cheng qi decoction" with many active ingredients including (emodin, baicalin, rhein, and chrysin) has been used for many years in west China hospitals for the reduction of the severity of AP through having an inhibitory effect on inflammatory parameters **[102]**. AP is associated with the secretion of pancreatic enzymes which cause autodigestion of pancreatic tissue, so antisecretory agents were investigated as potential therapies for AP. Somatostatin & its analog Octreotide are anti-secretory agents, that were used in China in the management of AP **[103]**, but they were not used in other countries due to inconclusive evidence **[104, 105]**. Digestive enzyme activation plays an essential role in the pathogenesis of AP. For this reason, protease inhibitors were investigated for their efficacy in AP like aprotinin **[106]**, gabexate mesylate (GM) **[107]** &Nafamostat mesylate (NM) but none of them were recommended for AP treatment **[108]**. The use of protease inhibitors was found to be ineffective in the treatment of AP **[109]**. Autophagy plays a key role in AP pathogenesis **[110]**. Pharmacological agents that inhibit the autophagy process provide a potential therapy for AP. In the AP model, spastin-1 treatment ameliorated the inflammation damage, such as infiltration of inflammatory cells, edema, degeneration & necrosis **[111]**. Spautin-A41 (a derivative of spastin-1) is a potent autophagy inhibitor. Treatment with spastin-A41 effectively ameliorated pancreatitis by inhibiting the formation of autophagosomes **[112]**. Phytochemicals like Artemisinin, Baicalin, Curcumin & Hesperidin are multi targets molecules derived from plants representing a new promising approach in the treatment of AP due to its ability to modulation of acinar cell death **[109]**.

Although till now there is no specific therapy for AP, researches are ongoing to explore potential treatment options. In A recent study **[113]**, a dietary isoflavone called Biochanin A (BCA) was explored for its effect against experimental AP. BCA effects in many diseases were evidenced such as acute lung injury **[114]** & acute hepatic injury **[115]**. BCA protective effect in AP was demonstrated by reducing pancreatic edema and reducing the production of serum pancreatic enzymes and pro-inflammatory

cytokines. In addition, BCA's beneficial effect on AP is partly mediated by improving intestinal homeostasis as evidenced by reduced serum amylase and lipase activities, and pancreatic edema **[113]**.

VB12 prevents AP in mice models, so it can be a promising treatment option for AP. clinical studies can be launched to test this beneficial effect on patients **[116]**. Diosgenin derivatives D (Drug D) are derivatives of Diosgenin (a kind of natural steroidal sapogenin) which has excellent anti-inflammatory properties and prevents AP through mitochondrial protection and PI3Kγ/Akt inhibition. Diosgenin derivatives D was explored for its beneficial effect on L-arginine-induced AP & its effect was demonstrated through mediating Gasdermin D (GSDMD) which causes holes in the acinar cells &release of inflammatory factors after accumulation in the Endoplasmic reticulum. Based on the fact that the inactivation of GSDMD significantly reduces necrosis and systemic inflammation in AP, drug D is expected to be a potentially effective therapeutic strategy for the development of new drugs **[117]**. A novel self-nanomicellizing formulation of EMP with phytochemical was examined for its effect on AP & it was found to suppress the effects of oxidative stress and inhibit proinflammatory cytokines **[118]**. Disulfiram was shown to inhibit NF-κB activation in acini & reduce expression of TLR4, so it was concluded that disulfiram ameliorates the severity of AP in mice **[119]**.

Conclusion

AP is a common disorder of the pancreas and could range from mild to potentially life-threatening cases. It has an increasing incidence rate and is associated with many complications that cause a high burden to the healthcare system. Animal models appear to be appropriate for the study of acute pancreatitis. The exact underlying pathophysiological mechanisms are not fully clear, but several studies on experimental models of acute pancreatitis have revealed many of those mechanisms that could be potential therapeutic targets. This is supported by the evidence that many processes are involved in animal models and humans, such as a strong inflammatory response. It was confirmed by elevated levels of many cytokines, including TNF-α and IL-1β. Other elevated factors include TLR4, NF-κB, and HMGB1. Autophagy and oxidative stress also play an important role in AP pathogenesis. In conclusion, there is an urgent need for the development of new therapeutic agents, and more research is required to reveal many unclear gaps.

Declarations

Consent to publish

All authors have read and agreed to the published version of the manuscript

Ethics approval and consent to participate

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article in the main manuscript.

Competing interests

No competing interests were declared by the authors

Funding statement

No funding source was received

Authors' contributions

Naglaa Gamal Ahmed: Writing - original draft, manuscript revision. Mariane G. Tadros: review the idea and outline & edit, and Supervision. Haidy E. Michelle: review & editing, Supervision. All authors approved the final manuscript.

5. References

1. Lee, P.J., G.I.J.N.r.G. Papachristou, and hepatology, New insights into acute pancreatitis. 2019. 16(8): p. 479-496 DOI: https://doi.org/10.1038/s41575-019-0158-2.
2. Lowenfels, A.B., P. Maisonneuve, and T.J.C.g.r. Sullivan, The changing character of acute pancreatitis: epidemiology, etiology, and prognosis. 2009. 11(2): p. 97-103DOI: https://doi.org/10.1007/s11894-009-0016-4.
3. Takeda, K., et al., Assessment of severity of acute pancreatitis according to new prognostic factors and CT grading. 2010. 17(1): p. 37-44 DOI: https://doi.org/10.1007/s00534-009-0213-4.
4. Cruz-Santamaría, D.M., C. Taxonera, and M.J.W.j.o.g.p. Giner, Update on pathogenesis and clinical management of acute pancreatitis. 2012. 3(3): p. 60 DOI: 10.4291/wjgp.v3.i3.60.
5. Karakahya, M., et al., The Histopathologic effects of L-Carnitine in a sodium Taurocholate–induced severe pancreatitis model. 2016. 101(5-6): p. 241-248 DOI: https://doi.org/10.9738/INTSURG-D-16-00058.1.
6. Krishna, S.G., et al., The changing epidemiology of acute pancreatitis hospitalizations: a decade of trends and the impact of chronic pancreatitis. 2017. 46(4): p. 482 DOI: 10.1097/MPA.0000000000000783.
7. Iannuzzi, J.P., et al., Global incidence of acute pancreatitis is increasing over time: a systematic review and meta-analysis. 2022. 162(1): p. 122-134 DOI: https://doi.org/10.1053/j.gastro.2021.09.043.
8. Tonsi, A.F., et al., Acute pancreatitis at the beginning of the 21st century: the state of the art. 2009. 15(24): p. 2945 DOI: 10.3748/wjg.15.2945.
9. Zheng, Y., et al., A multicenter study on etiology of acute pancreatitis in Beijing during 5 years. 2015. 44(3): p. 409-414 DOI: 10.1097/MPA.0000000000000273.
10. Sakorafas, G.H. and A.G.J.J.o.c.g. Tsiotou, Etiology and pathogenesis of acute pancreatitis: current concepts. 2000. 30(4): p. 343-356.
11. Toouli, J., et al., Guidelines for the management of acute pancreatitis. 2002. 17: p. S15-S39.
12. Li, J., et al., Calcium signaling of pancreatic acinar cells in the pathogenesis of pancreatitis. 2014. 20(43): p. 16146 DOI: 10.3748/wjg.v20.i43.16146.
13. Rinninella, E., et al., Nutritional support in acute pancreatitis: from physiopathology to practice. An evidence-based approach. 2017. 21(2): p. 421-432.
14. Biradar, S. and B.J.I.J.P.E.R. Veeresh, Pre-Clinical Evolutionary Study of Alpha-Pinene in L-Arginine Induced Acute Pancreatitis in Rat. 2013. 41: p. 73-8 DOI: 10.5530/ijper.47.4.10.
15. Granger, J. and D.J.S. Remick, Acute pancreatitis: models, markers, and mediators. 2005. 24: p. 45-51 DOI: 10.1097/01.shk.0000191413.94461.b0.
16. Beger, H.G., M. Büchler, and P. Malfertheiner, Standards in pancreatic surgery. 2012: Springer Science & Business Media.
17. Munoz, A. and D.A.J.A.f.p. Katerndahl, Diagnosis and management of acute pancreatitis. 2000. 62(1): p. 164-174.
18. Kusske, A., A. Rongione, and H.J.G. Reber, Cytokines and acute pancreatitis. 1996. 110(2): p. 639-642 DOI: https://doi.org/10.1053/gast.1996.v110.agast960639.
19. Pooran, N., et al., Cytokines (IL-6, IL-8, TNF): early and reliable predictors of

severe acute pancreatitis. 2003. 37(3): p. 263-266.

20. Formela, L., S. Galloway, and A.J.B.j.o.s. Kingsnorth, Inflammatory mediators in acute pancreatitis. 1995. 82(1): p. 6-13 DOI: https://doi.org/10.1002/bjs.1800820105.

21. Ang, A.D., et al., The effect of CSE gene deletion in caerulein-induced acute pancreatitis in the mouse. 2013. 305(10): p. G712-G721 DOI: https://doi.org/10.1152/ajpgi.00044.2013.

22. Warzecha, Z., et al., Therapeutic effect of ghrelin in the course of cerulein-induced acute pancreatitis in rats. 2010. 61(4): p. 419.

23. Rongione, A.J., et al., Interleukin 10 reduces the severity of acute pancreatitis in rats. 1997. 112(3): p. 960-967 DOI: https://doi.org/10.1053/gast.1997.v112.pm9041259.

24. Mayer, J., et al., Inflammatory mediators in human acute pancreatitis: clinical and pathophysiological implications. 2000. 47(4): p. 546-552 DOI: http://dx.doi.org/10.1136/gut.47.4.546.

25. Mofidi, R., et al., Association between early systemic inflammatory response, the severity of multiorgan dysfunction and death in acute pancreatitis. 2006. 93(6): p. 738-744 DOI: https://doi.org/10.1002/bjs.5290.

26. Malmstrøm, M.L., et al., Cytokines and organ failure in acute pancreatitis: inflammatory response in acute pancreatitis. 2012. 41(2): p. 271-277 DOI: 10.1097/MPA.0b013e3182240552.

27. Zhang, Q., et al., Changes of an inflammatory transmitter in acute necrotizing pancreatitis rat and effects of somatostatin. 1997. 5(3): p. 355.

28. Li, G., et al., TLR4-mediated NF-κB signaling pathway mediates HMGB1-induced pancreatic injury in mice with severe acute pancreatitis. 2016. 37(1): p. 99-107 DOI: https://doi.org/10.3892/ijmm.2015.2410.

29. Sawa, H., et al., Role of toll-like receptor 4 in the pathophysiology of severe acute pancreatitis in mice. 2007. 37(10): p. 867-873 DOI: https://doi.org/10.1007/s00595-007-3520-x.

30. Ding, J.-L., et al., Potential role of the TLR4/IRAK-4 signaling pathway in the pathophysiology of acute pancreatitis in mice. 2009. 58(11): p. 783-790 DOI: https://doi.org/10.1007/s00011-009-0048-0.

31. Yang, H.-L., et al., Coenzyme Q0 regulates NFκB/AP-1 activation and enhances Nrf2 stabilization in attenuation of LPS-induced inflammation and redox imbalance: Evidence from in vitro and in vivo studies. 2016. 1859(2): p. 246-261 DOI: https://doi.org/10.1016/j.bbagrm.2015.11.001.

32. Hayden, M.S. and S.J.C. Ghosh Shared principles in NF-κB signaling. 2008. 132(3): p. 344-362 DOI: https://doi.org/10.1016/j.cell.2008.01.020.

33. Jakkampudi, A., et al., NF-κB in acute pancreatitis: Mechanisms and therapeutic potential. 2016. 16(4): p. 477-488 DOI: https://doi.org/10.1016/j.pan.2016.05.001

34. Shi, Q., et al., Hydrogen-rich saline attenuates acute renal injury in sodium taurocholate-induced severe acute pancreatitis by inhibiting ROS and NF-κB pathway. 2015. 2015 DOI: https://doi.org/10.1155/2015/685043.

35. Zhang, T., et al., Sodium butyrate reduces organ injuries in mice with severe acute pancreatitis through inhibiting HMGB1 expression. 2015. 60(7): p. 1991-1999 DOI: https://doi.org/10.1007/s10620-015-3586-z.

36. Chen, S., et al., LincRNA-EPS alleviates severe acute pancreatitis by suppressing HMGB1-triggered inflammation in pancreatic macrophages. 2021. 163(2): p. 201-219 DOI: https://doi.org/10.1111/imm.13313.

37. Schoenberg, M.H., D. Birk, and H.G.J.T.A.j.o.c.n. Beger, Oxidative stress in acute and chronic pancreatitis. 1995. 62(6): p. 1306S-1314S DOI: https://doi.org/10.1093/ajcn/62.6.1306S .

38. Tsai, K., et al., Oxidative stress: an important phenomenon with pathogenetic significance in the progression of acute pancreatitis. 1998. 42(6): p. 850-855 DOI: http://dx.doi.org/10.1136/gut.42.6.850.

39. Sweiry, J. and G.J.S.J.o.G. Mann, Role of oxidative stress in the pathogenesis of acute pancreatitis. 1996. 31(sup219): p. 10-15 DOI: https://doi.org/10.3109/00365529609104992.

40. Zhou, J., et al., Norcantharidin: research advances in pharmaceutical activities and derivatives in recent years. 2020. 131: p. 110755 DOI: https://doi.org/10.1016/j.biopha.2020.110755.

41. Yang, S., et al., Autophagy regulation by the nuclear factor κB signal axis in acute pancreatitis. 2012. 41(3): p. 367-373 DOI: 10.1097/MPA.0b013e31822a9b05.

42. Yorimitsu, T., D.J.J.C.D. Klionsky, and Differentiation, Autophagy: molecular machinery for self-eating. 2005. 12(2): p. 1542-1552 DOI: https://doi.org/10.1038/sj.cdd.4401765.

43. Klionsky, D.J., et al., Guidelines for the use and interpretation of assays for monitoring autophagy. 2021. 17(1): p. 1-382 DOI: https://doi.org/10.1080/15548627.2020.1797280.

44. Mareninova, O.A., et al., Transgenic expression of GFP-LC3 perturbs autophagy in exocrine pancreas and acute pancreatitis responses in mice. 2020. 16(11): p. 2084-2097 DOI: https://doi.org/10.1080/15548627.2020.1715047.

45. Tang, D., et al., Endogenous HMGB1 regulates autophagy. 2010. 190(5): p. 881-892 DOI: https://doi.org/10.1083/jcb.200911078

46. Yu, X., et al., Emodin attenuates autophagy response to protect the pancreas from acute pancreatitis failure. 2018. 47(7): p. 892-897 DOI: 10.1097/MPA.0000000000001080.

47. Miracco, C., et al., Protein and mRNA expression of autophagy gene Beclin 1 in human brain tumors. 2007. 30(2): p. 429-436 DOI: https://doi.org/10.3892/ijo.30.2.429.

48. Kang, R., et al., HMGB1 as an autophagy sensor in oxidative stress. 2011. 7(8): p. 904-906 DOI: https://doi.org/10.4161/auto.7.8.15704.

49. Visconti, M., et al., The multiple-organ failure syndrome in acute pancreatitis. Its pathogenesis and treatment. 1995. 86(2): p. 81-85.

50. Bhatia, M.J.C.D.T.-I. and Allergy, Novel therapeutic targets for acute pancreatitis and associated multiple organ dysfunction syndrome. 2002. 1(4): p. 343-351 DOI: https://doi.org/10.2174/1568010023344517.

51. Zhu, A.-J., J.-S. Shi, and X.-J.J.W.j.o.g. Sun, Organ failure associated with severe acute pancreatitis. 2003. 9(11): p. 2570.

52. Al Mofleh, I.A.J.W.j.o.g.W., Severe acute pancreatitis: pathogenetic aspects and prognostic factors. 2008. 14(5): p. 675 DOI: 10.3748/wjg.14.675.

53. Hey-Hadavi, J., P. Velisetty, and S.J.P.M. Mhatre, Trends and recent developments in pharmacotherapy of acute pancreatitis. 2022: p. 1-11 DOI:

https://doi.org/10.1080/00325481.2022.2136390.

54. Ye, W., et al., Lipoxin A4 ameliorates acute pancreatitis-associated acute lung injury through the antioxidative and anti-inflammatory effects of the Nrf2 pathway. 2019. 2019 DOI: https://doi.org/10.1155/2019/2197017.
55. Wang, X., et al., Antioxidant and calcium channel blockers counteract endothelial barrier injury induced by acute pancreatitis in rats. 1995. 30(11): p. 1129-1136 DOI: https://doi.org/10.3109/00365529509101619.
56. Banks, P.A.J.G., Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. 2013. 62: p. 102-111.
57. Gorelick, F.S., et al., Do animal models of acute pancreatitis reproduce human disease? 2017. 4(2): p. 251-262 DOI: https://doi.org/10.1016/j.jcmgh.2017.05.007.
58. Harper, A. and H.S.J.T.J.o.p. Raper, Pancreozymin, a stimulant of the secretion of pancreatic enzymes in extracts of the small intestine. 1943. 102(1): p. 115 DOI: 10.1113/jphysiol.1943.sp004021.
59. Lampel, M. and H.F.J.V.A.A. Kern, Acute interstitial pancreatitis in the rat induced by excessive doses of a pancreatic secretagogue. 1977. 373(2): p. 97-117 DOI: https://doi.org/10.1007/BF00432156.
60. Pandol, S.J., et al., Animal and in vitro models of alcoholic pancreatitis: role of cholecystokinin. 2003. 27(4): p. 297-300.
61. Toma, H., et al., Nerve growth factor expression is up-regulated in the rat model of L-arginine–induced acute pancreatitis. 2000. 119(5): p. 1373-1381 DOI: https://doi.org/10.1053/gast.2000.19264.
62. Biczó, G., et al., The crucial role of early mitochondrial injury in L-lysine-induced acute pancreatitis. 2011. 15(10): p. 2669-2681 DOI: https://doi.org/10.1089/ars.2011.4065.
63. Rakonczay Jr, Z., et al., A new severe acute necrotizing pancreatitis model induced by L-ornithine in rats. 2008. 36(7): p. 2117 DOI: 10.1097/CCM.0b013e31817d7f5c.
64. Gu, P., et al., A novel label-free colorimetric detection of L-histidine using Cu2+-modulated G-quadruplex-based DNAzymes. 2018. 203: p. 195-200 DOI: https://doi.org/10.1016/j.saa.2018.05.084.
65. Mizunuma, T., S. Kawamura, and Y.J.T.J.o.n. Kishino, Effects of injecting excess arginine on rat pancreas. 1984. 114(3): p. 467-471 DOI: https://doi.org/10.1093/jn/114.3.467.
66. Hegyi, P., et al., L-arginine-induced experimental pancreatitis. 2004. 10(14): p. 2003 DOI: doi: 10.3748/wjg.v10.i14.2003.
67. Dawra, R., et al., Development of a new mouse model of acute pancreatitis induced by administration of L-arginine. 2007. 292(4): p. G1009-G1018 DOI: https://doi.org/10.1152/ajpgi.00167.2006.
68. Yang, X., et al., Experimental acute pancreatitis models: history, current status, and role in translational research. 2020. 11: p. 614591 DOI: https://doi.org/10.3389/fphys.2020.61459.
69. Su, K.H., C. Cuthbertson, and C.J.H. Christophi, Review of experimental animal models of acute pancreatitis. 2006. 8(4): p. 264-286 DOI: https://doi.org/10.1080/13651820500467358.
70. Rakonczay Jr, Z., et al., NF-κB activation is detrimental in arginine-induced acute

pancreatitis. 2003. 34(6): p. 696-709 DOI: https://doi.org/10.1016/S0891-5849(02)01373-4.

71. Kitajima, S. and Y.J.V.A.B. Kishino, Pancreatic damage produced by injecting excess lysine in rats. 1985. 49: p. 295-305 DOI: https://doi.org/10.1007/BF02912107.

72. Biczó, G., et al., Characterization of polyamine homeostasis in l-ornithine-induced acute pancreatitis in rats. 2010. 39(7): p. 1047-1056 DOI: 10.1097/MPA.0b013e3181d3cdf0.

73. Zhang, X., et al., Mechanisms of pancreatic injury induced by basic amino acids differ between L-Arginine, L-Ornithine, and L-Histidine. 2019. 9: p. 1922 DOI: https://doi.org/10.3389/fphys.2018.01922

74. Aho, H. and T.J.S.j.o.g. Nevalainen, Experimental pancreatitis in the rat: ultrastructure of sodium taurocholate-induced pancreatic lesions. 1980. 15(4): p. 417-424 DOI: https://doi.org/10.3109/00365528009181494.

75. Wittel, U.A., et al., Taurocholate-induced pancreatitis: a model of severe necrotizing pancreatitis in mice. 2008. 36(2): p. e9-e21 DOI: 10.1097/MPA.0b013e3181575103.

76. Chen, C., et al., Rosiglitazone attenuates the severity of sodium taurocholate-induced acute pancreatitis and pancreatitis-associated lung injury. 2009. 40(2): p. 79-88 DOI: https://doi.org/10.1016/j.arcmed.2008.11.004.

77. Liu, Z.-H., et al., A simple taurocholate-induced model of severe acute pancreatitis in rats. 2009. 15(45): p. 5732 DOI: 10.3748/wjg.15.5732.

78. Andrzejewska, A., et al., The effect of antecedent acute ethanol ingestion on the pancreas ultrastructure in taurocholate pancreatitis in rats. 1998. 65(2): p. 64-77 DOI: https://doi.org/10.1006/exmp.1998.2226.

79. Siech, M., P. Heinrich, and G.J.I.j.o.p. Letko, Development of acute pancreatitis in rats after single ethanol administration and induction of a pancreatic juice edema. 1991. 8(2): p. 169-175 DOI: https://doi.org/10.1007/BF02924430.

80. Letko, G., et al., Transition of rat pancreatic juice edema into acute pancreatitis by single ethanol administration. 1991. 187(2-3): p. 247-250 DOI: https://doi.org/10.1016/S0344-0338(11)80779-X.

81. Quon, M.G., et al., Chronic alcohol consumption intensifies caerulein-induced acute pancreatitis in the rat. 1992. 12(1): p. 31-39 DOI: https://doi.org/10.1007/BF02927068.

82. Katz, M., et al., Effect of ethanol on cholecystokinin-stimulated zymogen conversion in pancreatic acinar cells. 1996. 270(1): p. G171-G175 DOI: https://doi.org/10.1152/ajpgi.1996.270.1.G171.

83. Runkel, N., et al., Salmonella infection of the biliary and intestinal tract of wild opossums. 1991. 41(1): p. 54-56.

84. Gregerson, H., et al., Essentials of experimental surgery: Gastroenterology. 1996: CRC Press.

85. Lippi, G., M. Valentino, and G.J.C.r.i.c.l.s. Cervellin, Laboratory diagnosis of acute pancreatitis: in search of the Holy Grail. 2012. 49(1): p. 18-31 DOI: https://doi.org/10.3109/10408363.2012.658354.

86. Kiriyama, S., et al., New diagnostic criteria of acute pancreatitis. 2010. 17(1): p. 24-36 DOI: https://doi.org/10.1007/s00534-009-0214-3.

87. Cappell, M.S.J.M.C.o. N.A., Acute pancreatitis: etiology, clinical presentation, diagnosis, and therapy. 2008. 92(4): p. 889-923 DOI:

https://doi.org/10.1016/j.mcna.2008.04.013.

88. Beger, H.G. and B.M.J.W.j.o.g.W. Rau, Severe acute pancreatitis: clinical course and management. 2007. 13(38): p. 5043.

89. Wu, B.U. and P.A.J.G. Banks, Clinical management of patients with acute pancreatitis. 2013. 144(6): p. 1272-1281 DOI: https://doi.org/10.1053/j.gastro.2013.01.075.

90. Pitchumoni, C., N. Agarwal, and N.K.J.A.J.o.G. Jain, Systemic complications of acute pancreatitis. 1988. 83(6).

91. Vaughn, V.M., et al., Early versus delayed feeding in patients with acute pancreatitis: a systematic review. 2017. 166(12): p. 883-892 DOI: https://doi.org/10.7326/M16-2533.

92. Larino-Noia, J., et al., Early and/or immediately full caloric diet versus standard refeeding in mild acute pancreatitis: a randomized open-label trial. 2014. 14(3): p. 167-173 DOI: https://doi.org/10.1016/j.pan.2014.02.008

93. Machicado, J.D., et al., Practice patterns and utilization of tube feedings in acute pancreatitis patients at a large US referral center. 2018. 47(9): p. 1150 DOI: 10.1097/MPA.0000000000001141.

94. Kalfarentzos, F.E., et al., Total parenteral nutrition in severe acute pancreatitis. 1991. 10(2): p. 156-162 DOI: https://doi.org/10.1080/07315724.1991.10718140.

95. Yousaf, M., K. McCallion, and T.J.J.o.B.S. Diamond, Management of severe acute pancreatitis. 2003. 90(4): p. 407-420 DOI: https://doi.org/10.1002/bjs.4179.

96. Tenner, S., et al., American College of Gastroenterology guideline: management of acute pancreatitis. 2013. 108(9): p. 1400-1415 DOI: 10.1038/ajg.2013.218.

97. Lee, S.H., et al., Revised Clinical Practice Guidelines of the Korean Pancreatobiliary Association for Acute Pancreatitis. 2023. 17(1): p. 34-48 DOI: https://doi.org/10.5009/gnl220108.

98. Párniczky, A., et al., Antibiotic therapy in acute pancreatitis: From global overuse to evidence-based recommendations. 2019. 19(4): p. 488-499 DOI: https://doi.org/10.1016/j.pan.2019.04.003.

99. Chatila, A.T., M. Bilal, and P.J.W.j.o.c.c. Guturu, Evaluation, and management of acute pancreatitis. 2019. 7(9): p. 1006 DOI: 10.12998/which.v7.i9.1006.

100. Yildirim, A., et al., The effects of glycyrrhizin on experimental acute pancreatitis in rats. 2013. 17(22): p. 2981-2987.

101. Pan, Y.J.E.R.M.P.S., The effects of glycyrrhizin on acute pancreatitis in mice. 2014. 18(24): p. 3943-3947.

102. Wen, Y., et al., Chaiqin cheng qi decoction alleviates the severity of acute pancreatitis via inhibition of TLR4 and NLRP3 inflammasome: identification of bioactive ingredients via pharmacological sub-network analysis and experimental validation. 2020. 79: p. 153328 DOI: https://doi.org/10.1016/j.phymed.2020.153328.

103. Mao, X. and Z.J.A.P.M. Yang, Current usage status of somatostatin and its analogs and trypsin inhibitors: a real-world study of 34,654 Chinese adult patients with acute pancreatitis. 2021. 10(2): p. 1325-1335 DOI: 10.21037/APM-19-363.

104. Sun, C., et al., Current diagnosis and treatment of acute pancreatitis in China: a real-world, multicenter study. 2021. 21(1): p. 210 DOI: https://doi.org/10.1186/s12876-021-01799-1.

105. Moggia, E., et al., Pharmacological interventions for acute pancreatitis. 2017(4) DOI: https://doi.org/10.1002/14651858.CD011384.

106. AMMANN, R. and J.J.D.M.W. MEIER, APROTININ IN THE TREATMENT OF ACUTE-PANCREATITIS. 1987. 112(35): p. 1355-1355.

107. Valderrama, R., et al., Multicenter double-blind trial of gabexate mesylate (FOY) in unselected patients with acute pancreatitis. 1992. 51(2): p. 65-70 DOI: https://doi.org/10.1159/000200877.

108. Kambhampati, S., W. Park, and A.J.W.j.o.g.W. Habtezion, Pharmacologic therapy for acute pancreatitis. 2014. 20(45): p. 16868 DOI: 10.3748/wjg.v20.i45.16868.

109. Sundar, V., et al., Current trends in pharmacological approaches for treatment and management of acute pancreatitis–a review. 2020. 72(6): p. 761-775 DOI: https://doi.org/10.1111/jphp.13229.

110. Hirota, M., et al., Continuous regional arterial infusion versus intravenous administration of the protease inhibitor nafamostat mesylate for predicted severe acute pancreatitis: a multicenter, randomized, open-label, phase 2 trial. 2020. 55: p. 342-352 DOI: https://doi.org/10.1007/s00535-019-01644-z.

111. Xiao, J., et al., Spautin-1 ameliorates acute pancreatitis via inhibiting impaired autophagy and alleviating calcium overload. 2016. 22(1): p. 643-652 DOI: https://doi.org/10.2119/molmed.2016.00034.

112. Dong, K., et al., Spautin-A41 attenuates cerulein-induced acute pancreatitis through inhibition of dysregulated autophagy. 2019. 42(11): p. 1789-1798 DOI: https://doi.org/10.1248/bpb.b19-00132.

113. Pan, X., et al., Biochanin A ameliorates caerulein-induced acute pancreatitis and associated intestinal injury in mice by inhibiting TLR4 signaling. 2023. 113: p. 109229 DOI: https://doi.org/10.1016/j.jnutbio.2022.109229.

114. Hu, X., et al., Biochanin A protects against lipopolysaccharide-induced acute lung injury in mice by regulating TLR4/NF-κB and PPAR-γ pathway. 2020. 138: p. 103846 DOI: https://doi.org/10.1016/j.micpath.2019.103846.

115. Alipour, M.R. and E.J.C.-B.I. Karimi-Sales, Molecular mechanisms of protective roles of isoflavones against chemicals-induced liver injuries. 2020. 329: p. 109213 DOI: https://doi.org/10.1016/j.cbi.2020.109213

116. Chen, Y., et al., Vitamin B12 Serves Potentially as a Preventative and Therapeutic Agent for Acute Pancreatitis DOI: http://dx.doi.org/10.2139/ssrn.4323976.

117. Zhang, C., et al., Drug D, a diosgenin derive, inhibits L-arginine-induced acute pancreatitis through meditating GSDMD in the endoplasmic reticulum via the TXNIP/HIF-1α pathway. 2022. 14(13): p. 2591 DOI: https://doi.org/10.3390/nu14132591.

118. Li, Q., et al., A novel self-nanomicellizing system of empagliflozin for oral treatment of acute pancreatitis: An experimental study. 2022. 42: p. 102534 DOI: https://doi.org/10.1016/j.nano.2022.102534.

119. Huang, Q.-Y., et al., Disulfiram reduces the severity of mouse acute pancreatitis by inhibiting RIPK1-dependent acinar cell necrosis. 2023: p. 106382 DOI: https://doi.org/10.1016/j.bioorg.2023.106382.