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Review

Current trends in pharmacological approaches for treatment and management of acute pancreatitis – a review

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Abstract

Objectives Acute pancreatitis (AP) is an inimical disorder associated with overall mortality rates between 10-15%. It is a disorder of the exocrine pancreas which is characterized by local and systemic inflammatory responses primarily driven by oxidative stress and death of pancreatic acinar cells. The severity of AP ranges from mild pancreatic edema with complete recuperative possibilities to serious systemic inflammatory response resulting in peripancreatic/pancreatic necrosis, multiple organ failure, and death.

Key findings We have retrieved the potential alternative approaches that are developed lately for efficacious treatment of AP from the currently available literature and recently reported experimental studies. This review summarizes the need for alternative approaches and combinatorial treatment strategies to deal with AP based on literature search using specific key words in PubMed and ScienceDirect databases.

Summary Since AP results from perturbations of multiple signaling pathways, the so called "monotargeted smart drugs" of the past decade is highly unlikely to be effective. Also, the conventional treatment approaches were mainly involved in providing palliative care instead of curing the disease. Hence, many researchers are beginning to focus on developing alternate therapies to treat AP effectively. This review also summarizes the recent trends in the combinatorial approaches available for AP treatment.

Introduction

Acute pancreatitis (AP) is an inflammatory disorder of pancreas which is characterized by severe epigastric pain and increased/irregular secretion of pancreatic enzymes, associated with involvement of multiple systems. The pancreatic acinar cells (PACs) in the exocrine pancreas secrete zymogens (inactive digestive enzymes) namely prolipase, trypsinogen and amylase into the pancreatic ducts. Usually, these zymogens are activated in duodenum. When the premature activation of these zymogens occurs in the PACs, it results in the digestion of pancreas itself. This self-digestive condition leads to inflammation, oedema, haemorrhage and necrosis which underlies the inimical pathology of AP. AP is exacerbated by the release of pro-inflammatory mediators such as tumour necrosis factor-α (TNF-α), interleukin (IL)-6 and IL-1β by the injured PACs further aggravating the forward inflammatory responses as shown in Figure 1.

The pathogenesis of AP is a sequential process which begins as an inflammatory response by host immune cells leading to the production of pro-inflammatory cytokines and chemokines. Once the disease process is initiated, there is an elevation in levels of inflammatory mediators such as TNF-α, interleukin-1 (IL-1) and monocyte chemoattractant protein (MCP-1).[1,2] In order to subside the tissue insults, these initially evoked pro-inflammatory responses are counteracted by a compensatory anti-inflammatory response (CARS). CARS results in release of anti-inflammatory cytokines like IL-10 thus maintaining the equilibrium between pro-inflammatory and anti-inflammatory responses in the body.[3] However, an overactive

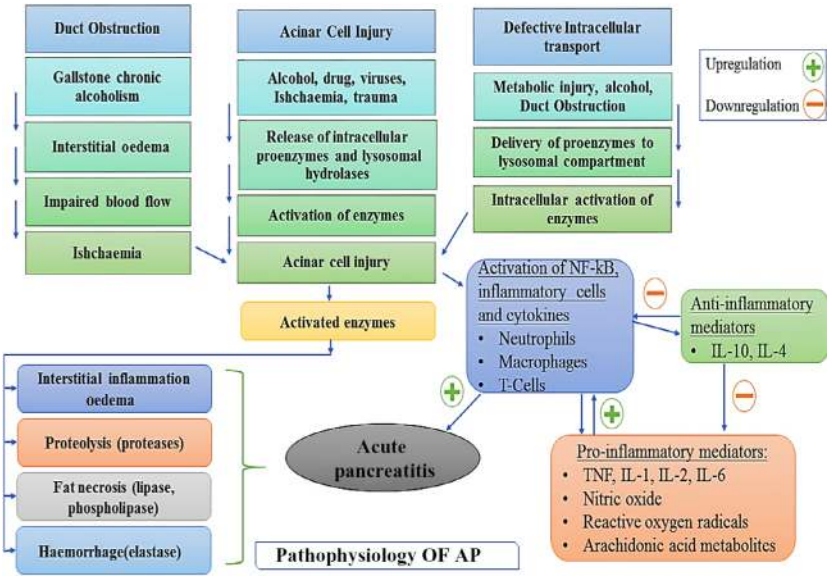

Figure 1 Pathophysiology of acute pancreatitis. The figure illustrates the pathophysiological mechanism in acute pancreatitis and different triggers and stimulants of pro and/or anti-inflammatory cytokine release leading to acinar cell injury finally resulting in autodigestion of pancreas/acute pancreatitis. [Colour figure can be viewed at wileyonlinelibrary.com]

inflammatory response mediated by the excess release of cytokines and chemokines is accompanied by systemic inflammatory response syndrome (SIRS). Since macrophages coordinate both the commencement and the resolution of inflammation, activation of macrophages determines the degree of inflammatory response in AP.[4] As the disease further progresses by recruiting more inflammatory cells, the distant organs including lungs, kidney and liver are affected.[5,6] AP progresses usually after the second week of disease onset, leading to necrotizing pancreatitis, chronic pancreatitis (CP) further progressing to sepsis, multiorgan dysfunction syndrome (MODS) and finally death.[6] Moreover, the AP severity is also determined by the death of PACs. Both apoptosis and necrosis of PACs are reported in clinical and experimental AP.[7] The extent of the disease severity greatly depends upon the balance between apoptosis and necrosis of the injured acinar cells. Hence, the agents that induce apoptosis of injured PACs and activated macrophages could be potential therapeutic intervention for AP.

Since AP results from the perturbations of multiple signalling pathways, the so-called 'monotargeted smart drugs' of the past decade is highly unlikely to be effective. With increasing incidences of AP worldwide, there is a need for more effective therapeutic approaches for management of AP. Also, the conventional treatment approaches were mainly involved in providing palliative care instead of curing the disease. Also, AP arises primarily in response to lifestyle and dietary consumption such as high fat diet and alcohol consumption or prolonged exposure to bile acid because of gallstones.[8] Hence, many researchers are beginning to focus on developing alternative therapies to treat AP effectively. This review summarizes the recent trends in the alternative approaches available for AP treatment. The following sections mainly discuss some of the recent approaches for more effective clinical treatment of AP. Elucidation of the interplay between the signalling pathways, immune cells and inflammatory mediators involved in AP helps to identify clinically effective therapeutic strategies and also will provide new insights for the enhancement of existing therapeutic strategies.

Anticytokine therapy in AP

Several inflammatory mediators such as cytokines, chemokines, neuropeptide and gaseous mediators are excellent therapeutic targets for AP and associated lung injury (ALI). The pro-inflammatory cytokines are the first-line molecules that are released at the onset and during the course of AP. It is reported that the serum levels of TNFα correlate with the clinical outcome of AP.[9] TNFα stimulates its initial pro-inflammatory effect by binding to its cell surface receptors TNFR1 and TNFR2 and initiates the activation of associated signalling pathways. Inhibiting the activity of TNFα by anticytokine therapy such as infliximab (anti-TNFα monoclonal antibody) reduced the systemic inflammatory response and is associated with a moderate decrease in mortality in experimental pancreatitis.[10] Also, the genetic deletion of TNFR1 revealed an anti-inflammatory effect against cerulein-stimulated AP.[11]

In human severe acute pancreatitis (SAP), serum IL-6, belonging to the family of gp130 ligands, is a reliable marker for AP severity and a reliable predictor of ALI. It has been reported that IL-6 also exerts its pro-inflammatory effects through the Jak-2-dependent STAT3 pathway in C57BL/6 and $Il6^{-/-}$ mice pancreas. The results of this study suggest that $Il6^{-/-}$ mice attenuated AP by suppressing the STAT3 activity.[12]

Many more cytokines and chemokines are also involved in various phases of the progression of AP. For instance, targeting the monocyte chemoattractant protein (MCP-1) and regulated on activation normal T cell expressed and secreted (RANTES) released by the rat PACs showed possible reduction in cholecystokinin (CCK) and ethanol-induced AP and ALI.[13] For example, Met-RANTES which acts as the chemokine receptor RANTES antagonist reduces the risk for systemic complications by reducing the lung injury.[14,15]

Although anticytokine therapies attenuate the SIRS during AP, it compromises with the innate immune responses against the microbial infections. For instance, TNF-α neutralization impairs the innate immunity against intracellular pathogens.[16] Thus, anti-TNF-α therapy increases the risk for mortality during sepsis, in which microbial growth contributes to the disease pathogenesis.

Targeting abnormal calcium signalling and mitochondrial injury

While there are various other factors that can trigger AP, pancreatic pathology appears to converge with the dysregulation of Ca^{2+} homeostasis, premature activation of intracellular protease and the decreased ATP production. The dysregulation of Ca^{2+} homeostasis and decreased ATP production are dependent to each other and are important factors in the regulation of AP. The excessive release of Ca^{2+} through Ca^{2+} channels such as ryanodine receptors (RyRs), inositol 1,4,5-trisphosphate receptors (IP3Rs) and two-pore channels type 2 (TPC2) additionally with the subsequent influx of Ca^{2+} from Orai channels and the impairment of Ca^{2+} extrusion mechanism perturbate the – Ca^{2+} signalling pathways. Also, there is an intimate linkage between Ca^{2+} homeostasis and ATP. The ATP-dependent Ca^{2+} transport systems such as SERCA (sarco/endoplasmic reticulum Ca^{2+} ATPases), PMCA (plasma membrane Ca^{2+} ATPases) and SPCA (secretory pathway Ca^{2+} ATPases) maintain the steep Ca^{2+} gradients existing between the cytosol, other organelles (Golgi apparatus and endoplasmic reticulum) and the extracellular environment (Figure 2).

Excessive Ca^{2+} release provoked during AP will draw out more ATP consumption in a trail to maintain Ca^{2+} homeostasis in acinar cells and thus have a significant impact on the ATP levels in the cells.[17] The mitochondrial enzymes balancing the energy needs through production of ATP are also Ca^{2+} dependent. Therefore, Ca^{2+} overload in mitochondria will result in potential mitochondria collapse, opening of the permeability transition pore (mPTP), the suspension of ATP production and triggering of apoptotic cell death. In this regard, some of the previously reported strategies to treat AP by inhibiting the Ca^{2+} channels, RyRs, IP3Rs, Orai1 with the help of calcium channel blockers.[18–20] Unfortunately, restoring ATP supply solely using these strategies did not prove to be very effective.

Acute pancreatitis, due to excessive alcohol consumption, is primarily caused by its non-oxidative and oxidative metabolism. In non-oxidative conditions, the alcohol metabolism leads to increase in the levels of fatty acid ethyl ester (FAEE), while in oxidative metabolism, it leads to the accumulation of acetate, acetaldehyde and NADH.[21] The FAEEs cause deleterious effects such as the zymogen activation,[19] calcium homeostasis disruption in acinar cells[22] and transcription factors (NF-κB and AP-1) activation.[23] Besides acetaldehyde from oxidative metabolism enhances the activation of transcription factors, resulting in overproduction of pro-inflammatory cytokines. Also, alcohol diminishes the [NAD]/[NADH] ratio and increases the [lactate]/[pyruvate] ratio altering the intracellular redox state leading to PAC injury.[24]

The ductal obstruction by gallstones leads to increase in duct pressure and exposure of acinar cells to bile acids, blocking acinar exocytosis and leading to the premature activation of pancreatic enzymes.[25] This premature activation, disruptions in calcium homeostasis and activation of apoptotic pathways are the early events in AP causing inflammation in the pancreas. These early events will lead to local and systemic complication such as organ failure and death by activation of various pathophysiological pathways. This progression is mediated by pro-inflammatory cytokines, reactive oxygen species (ROS), chemokines, platelet-activating factor, Ca2þ, adenosine, vascular and neuronal responses as shown in Figure 1.[26]

Oxidative stress and redox reactions are predominantly involved in the systemic inflammatory response development because of xanthine oxidase activation, glutathione depletion and thiol oxidation in proteins which are the critical features of AP. Also, the ascitic fluid in severe necrotizing pancreatitis releases extracellular haemoglobin into the circulation resulting in the enhancement of lipid peroxidation in the plasma and inflammatory infiltration into the lung tissues. It also enhances the gene expression of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF). This upregulates the HIF-VEGF pathway leading to increased angiogenesis thus resulting in systemic inflammatory response in lungs.

Besides the causative agents, an early inflammatory reaction in acinar cells is characterized by NF-κB activation and

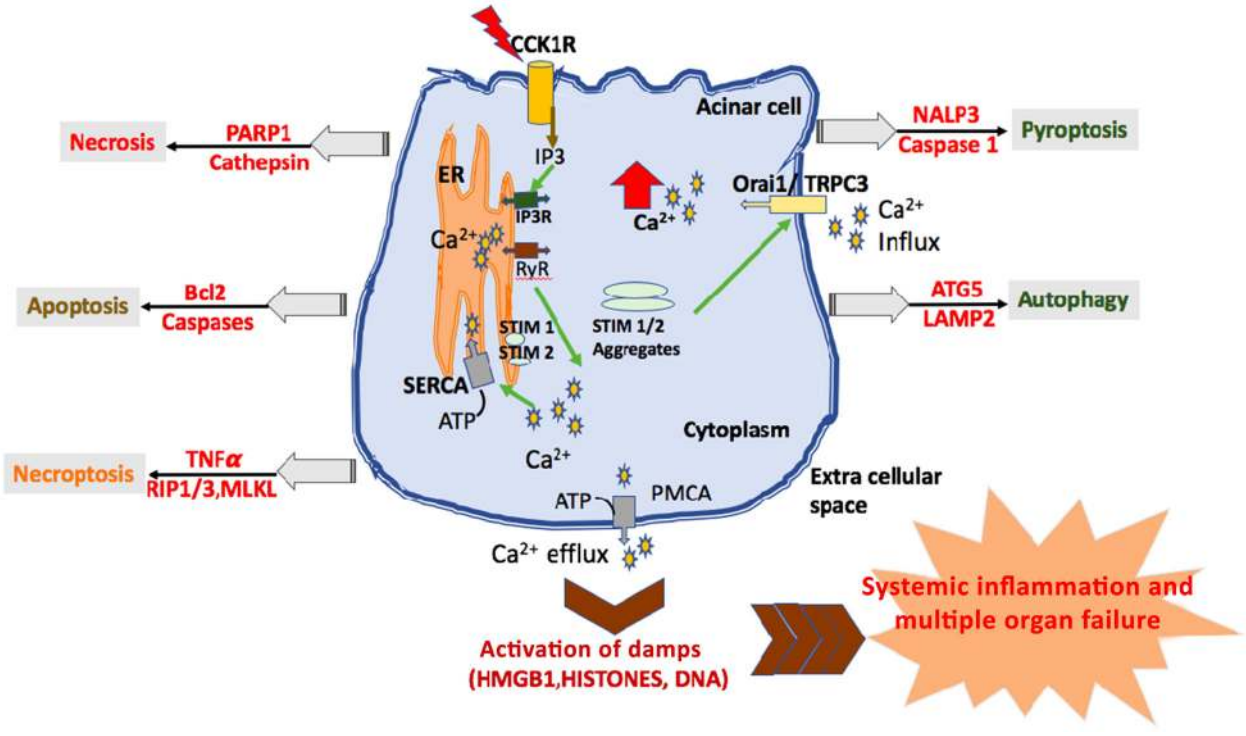

Figure 2 Therapeutic targets in impaired Ca^{2+} signalling in acute pancreatitis. The figure depicts the role of various therapeutic targets pertaining to the Ca^{2+} signalling in acute pancreatitis. The excessive release of Ca^{2+} during acute pancreatitis through Ca^{2+} channels such as RyRs, IP3Rs and TPC2 along with Ca^{2+} influx from Orai channels disrupts the Ca^{2+} signalling pathways. The ATP-dependent Ca^{2+} transport systems such as SERCA, PMCA maintains the Ca^{2+} levels and restores the existing balance between the cytosol and other organelles like endoplasmic reticulum. [Colour figure can be viewed at wileyonlinelibrary.com]

cytokines production in acinar cells which are partly independent of trypsinogen activation.[27] As a result, inflammatory cells such as monocytes and neutrophils are activated and recruited to pancreas. Neutrophils are found to enhance the premature activation of trypsinogen. This induces tissue damage as well as inflammation in the pancreas.[28]

Targeting cell death and damage-associated molecular pattern molecules (DAMPs) in AP

The mitochondrial dysfunction and endoplasmic reticulum (ER) stress during to AP activate various events like oxidative stress and calcium overload. These pathological events are common triggers of cell death such as apoptosis, necrosis, necroptosis, pyroptosis and autophagy depending on the regulator or effector proteins triggered. Unlike the intracellular DAMPs, the extracellular physiological role of DAMPs is important mediators of local and systemic inflammatory responses. DAMPs such as high mobility group box 1 (HMGB1), DNA, HSPs, histones and ATP link pancreatic tissue injury to SIRS, which leads to subsequent MODS and even death. For example, under normal physiological conditions, HMGB1 is located in the nucleus of PACs to maintain nucleosome stability. However, during AP, increased oxidative stress and calcium overload leads to HMGB1 release from the nucleus. Loss of intracellular HMGB1 in PACs promotes DNA damage, cell death and histone release. Subsequently, extracellular histone recruits macrophages and neutrophils which leads to more HMGB1 release. Thus, circulating HMGB1 levels are increased and function as a mediator of SIRS in AP.

Dying PACs release DAMPs promoting infiltration of various immune cells including neutrophils, monocytes and macrophages. During AP, DAMPs-activated nuclear factor-κB (NF-κB), mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription 3 (STAT3) promote inflammatory responses leading to disease progression.[29] Antioxidants and anticoagulants like antithrombin III and danaparoid sodium inhibit HMGB1 release and therefore protect against injury in AP.[30,31] Unfortunately, it is also observed that PACs undergoing apoptosis can also release histones, DNA and HMGB1, which accelerates pancreatic injury and the inflammatory response. Hence, the beneficial effect induction or inhibition of apoptosis in a clinical setting remains unknown. In

addition, the current pharmacologic agents that target apoptosis largely lack specificity.

One early pathological event of AP is the accumulation of large autophagic vacuoles in PACs. Due to faulty autophagic flux, formation of acinar cell vacuoles, activation of trypsinogen, initiation of cell death and the inflammatory response occur. Yet, in contrast, ATG5-mediated autophagosome formation in PACs aggravates AP as blocking autophagy reduces trypsinogen activation in ATG5-deficient mice and protects the mice against the cerulein-induced AP.[32] In addition, lysosomal dysfunction from loss of lysosomal membrane protein (LAMP)-2 can lead to impairment in autophagic flux. During AP, LAMP-2 deficiency impairs the autophagosome–lysosome fusion promoting necrosis and inflammatory response along with HMGB1 release in AP.[33] Besides, death receptors that triggered upon inhibition of caspase-8 and binding of TNF-α, FasL and TNF-related apoptosis-inducing ligand (TRAIL) under apoptosis-deficient conditions (e.g. pan-caspase inhibitor Z-VAD-FMK) may promote necroptosis. Necroptosis is mainly regulated by receptor-interacting protein (RIP) kinases. The RIP kinases are caspase-8 substrates that activates NF-κB and other death-inducing signals in AP.[34] RIP1/RIPK-1 fuses to the RIP3/RIPK-3 to create a phosphorylation complex and assembles the necrosome. Therefore, genetic or pharmacological inhibition of caspase-8 activity affects the FAS-associated death domain protein (FADD) and strengthens the RIP1 stability and thus induces necroptosis.[29] Specifically, necrostatin-1 which is a RIP1-specific kinase inhibitor selectively inhibits necroptosis and reduces the severity of the AP.[29,35]

There are other types of cell death, like pyroptosis, which is a highly specialized form of inflammatory lytic programmed cell death mediated by caspases. Inflammasomes and stimulated innate immunity activate caspase-1 or caspase-11, 4, or 5, leading to the formation of large pores in the membrane, cell swelling and membrane rupture. In AP, TLR9 gene deletion leads to impairment in the inflammasome pathway and decreases the cell death processes.[36] These data highlight the importance of regulatory switches between different forms of cell death that influence the development of AP. Yet, these pharmacological targets are solely not sufficient to control the disease as the beneficial effect of targeting the cell death mechanism is clinically unproven.

Targeting the premature activation of intracellular proteases

Although the current treatment approaches focus on palliative care, these treatment strategies fail to control the disease. The premature activation of trypsinogen into trypsin in the PACs is the prime event in the early pathogenesis of AP resulting in the consecutive events of autodigestion of the pancreas.[37,38] Hence, many research studies involving the use of protease inhibitor were attempted. For instance, gabexate mesylate (GM) is a protease inhibitor used in the treatment of AP in some countries. This treatment is based on the evidence claiming that autodigestion of pancreas by premature activation of pancreatic enzymes is the key event in AP. However, the Food and Drug Administration (FDA) has not recommended or approved its clinical use as it showed no or little therapeutic effect on AP patients.[39] Protease inhibitors themselves also resulted in the production of inflammatory cytokines which in turn attribute to the disease progression resulting in SAP. As a consequence, the use of protease inhibitors was found to be ineffective in the treatment of AP.

Due to its wide variations in clinical outcome, the treatment of AP requires a combinatorial approach. The therapeutic approaches used so far to treat AP include intravenous fluid replacement, analgesics, dietary changes, calcium ion antagonists, pancreatic secretion inhibitors (somatostatin and its analogue octreotide), L-arginine and inhibitors of various inflammatory mediators and surgically removing the devitalized tissues. Unfortunately, these methods were not fully effective and the existing drugs have shortened half-life and limited clinical efficiency. They have low bioavailability and in unlikely conditions, they too evoke pro-inflammatory responses. Some approaches involving the use of antioxidants alone to treat AP were attempted but the results were not fruitful. Current consensus is that the antioxidants may be used along with direct anti-inflammatory therapy to get significant results.[40] Consequently, in the quest to find more efficient treatment strategies for AP, the researchers and clinicians are beginning to focus on cellular therapies, phytotherapies and nanotechnological applications owing to their enormous potential. Nanotechnology can be employed to enhance the physiochemical properties of the potent anti-inflammatory agents. They can resolve problems associated with non-effective modalities like poor aqueous solubility, off-site nonspecific targeting, prolonged circulation time, as well as image guidance.

Phytotherapy on the other hand involves pleiotropic natural products that can be used to target several deleterious signalling proteins involved in AP, suppression of neutrophil infiltration and inhibition of inflammasome complex. These compounds also possess antioxidant activity.[41] Apart from that, cell therapies involving mesenchymal stem cells (MSCs) can reduce acute inflammatory response with the help of their immunomodulatory effects such as suppression of pro-inflammatory cytokines, secretion of anti-inflammatory cytokines and regulation of immune cell activation and proliferation.[42] Hence, these approaches may serve as a potential treatment method for AP in future.

Targeting micro-RNA in AP

The micro-RNA (mi-RNA) is a single-stranded non-coding RNA that controls the expression of several inflammatory genes through either cleavage or translational repression. It has been reported that during AP animal model, the plasma levels of miR-216a, miR-216b and miR217 are reported to be significantly elevated.[43–45] The TGF-β promotes AP by up-regulating miR-216a and targets PTEN (phosphatase and tensin homolog) which acts as a suppressor in the PI3K/Akt signalling.[46] Further, mi-RNs also regulate the NF-κB mediated inflammatory responses in AP. Reports suggest that mi-R-126-5p, mi-R-148a-3p, mi-R-216a5p, mi-R-551b-5p and mi-R-375 are found abundantly in the serum of SAP patients whereas mi-R-216a-5p, mi-R-551b-5p and miR-375 are highly expressed in mild AP patients.[47]

Yet, the major challenge in therapeutically targeting mi-RNA is that a single mi-RNA regulates multiple downstream targets simultaneously and will potentially result in undesired or unexpected therapeutic effects, especially when systemic drug delivery is used. Therefore, a personalized mi-RNA therapy to overcome the undesired side effects is required in the future.

Reports on potential therapeutic approaches against AP

The possibilities and current trends in AP treatment approaches are discussed below in this section (Figure 3).

Phytotherapy

Phytoceuticals (pleiotropic multitarget molecules) derived from plants represent an attractive trend in the therapeutic approach towards pancreatitis. These molecules are found to have pancreas protective potential whose efficacy is based on their ability to modulate acinar cell death. These phytoceuticals come under diverse classes such as flavonoids, anthraquinones, polyphenols, lignans, sesquiterpene lactones, alkaloids and nitriles. These compounds maintain the balance between necrosis and apoptosis via either activating apoptosis by mechanisms such as upregulation of *FasL* gene expression, inhibition of X-linked inhibitor of apoptotic proteins or inhibiting necrosis resulting in significant decrease in the severity of the disease.[41] They also have antioxidant activity and exhibit specific protective activity such as suppression of neutrophil infiltration and inflammasome inhibition. The various potent phytochemicals to treat pancreatitis and their mechanism of action are described in Table 1.

Despite their potential as a treatment for AP, they do possess some disadvantages such as the low bioavailability, low solubility (e.g. curcumin)[48] or rapid sulfate conjugation at liver/intestine (e.g. resveratrol).[49] Some effective solutions were already proposed such as the use of bioenhancers like piperine or altered using nanotechnology to effectively increase bioavailability and solubility. Also, combined administration of synthetic drug with phytochemicals or combining several phytochemicals together for overcoming the disadvantages, thereby providing efficient

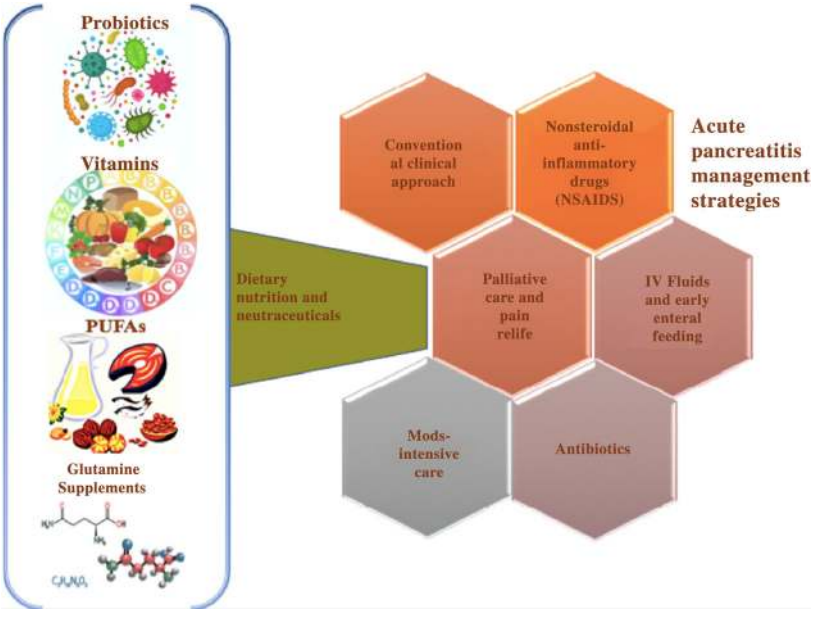

Figure 3 Acute pancreatitis management strategies. The figure depicts the current treatment strategies available for treatment of acute pancreatitis including the new combinatorial pharmacological approaches. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 1 Potential phytochemicals to treat AP and their possible mechanism of action

S. no	Phytochemical	*In-vivo/in-vitro* experimentation	Therapeutic mechanism/principle in AP	References
1.	Artemisinin Derived from: *Artemisia annua* Derivatives: Artesunate, Arteether, Hydroartemisinin and Artemether	Cerulein-induced AP of Wistar rats PACs- inflammation induced by treating with lipopolysaccharide (LPS) Rats with 3.5% sodium taurocholate-induced SAP	Artemisinin: Reduced the severity by increasing caspase-3 activity and the number of apoptotic cells, while reducing serum amylase level and the number of necrotic cells Also, Artemisinin decreased inflammatory cell infiltration and pancreatic oedema, MIP-1α protein, NF-κB activation, IL-1β mRNA and myeloperoxidase (MPO) Artesunate: exhibited substantial inhibition in the expression of IL-1β, NF-κB p65, TLR4 and IL-6 but it did not significantly influence the TNF-α release Artesunate was also effective in increasing the survival rate by decreasing lipase and serum amylase activity, ameliorating pancreatic histological alterations (haemorrhages and necrosis) and pancreatic release of pro-inflammatory cytokines namely IL-6 and IL-1β	[97] [98] [98]
2.	Baicalin Derived from: *Erigeron breviscapus* And *Scutellaria* spp	LPS induced inflammation in RAW264.7 (macrophage-type) cells Rats with SAP	Blocked the synthesis of pro-inflammatory mediators [endothelin-1 (ET-1), tumour necrosis factor α (TNF-α) and thromboxane A2 (TXA2)] and macrophage activation. It also hindered ROS generation by increasing intracellular SOD (superoxide dismutase) Decreased inflammatory response indicated by lower levels of inflammation markers (TNF-α, IL-6) and leucocyte recruitment (P-selectin- involved in platelets aggregation). This effect is achieved through the downregulation of activators namely PLA2, TLR4 and ET-1. It promotes apoptosis through activation of caspase-3 and by increasing the Bax protein expression	[99–101]
3.	Crambene Derived from: Breakdown product of (epi) progoitrin glucosinolates found in cruciferous plants	Isolated pancreatic acinar cells	Crambene induced apoptosis in pancreatic acinar cells (confirmed by increased caspase activation). It induced the collapse of mitochondrial membrane potential, followed by cytochrome *c* release suggesting the involvement of the apoptosis intrinsic pathway. CD36-positive macrophages might play a major role in phagocytosis by suppressing the inflammatory response by increasing anti-inflammatory cytokine IL-10 release Decreased inflammatory response indicated by lower levels of inflammation markers (TNF-α, IL-6) and leucocyte recruitment (P-selectin- involved in platelets aggregation). This effect is achieved through the downregulation of activators namely PLA2, TLR4 and ET-1. It promotes apoptosis through activation of caspase-3 and by increasing the Bax protein expression	[102]
4.	Curcumin Derived from: *Curcuma longa* and other related species	Pancreatitis animal models	Curcumin promotes apoptosis by caspase-3 activation. Curcumin reduces the pancreatic injury and ameliorates the deleterious effects of pancreatitis on other organs, as reflected by lower activity of pancreatic enzymes trypsin, amylase, lipase and decrease in transaminases levels respectively. It also decreases the activity of the enzymes responsible for the oxidative aggression	[103]
5.	Embelin Derived from: *Ardisia japonica, Embelia ribes, Embelia schimperi*	Mouse pancreatitis model induced by cerulein	It is a potent inhibitor of survival associated protein XIAP, owing to its ability to bind the Baculovirus Inhibitor of apoptosis protein Repeat 3 (BIR3) domain of XIAP (caspase-9 binding site), thus, preventing the interaction of XIAP with caspase-9 Subcutaneous injection of embelin (20 mg/kg) for 5 days showed significant increase in the caspase-9, caspase-3 and caspase-8 activity levels leading to a threefold increase in apoptosis	[104] [105]

Table 1 (*Continued*)

S. no	Phytochemical	*In-vivo*/*in-vitro* experimentation	Therapeutic mechanism/principle in AP	References
6.	Emodin Derived from: *Rheum* spp, *Rhamnus* spp, *Fallopia japonica*	Rat phagocyte cells pMΦs	Emodin has the ability to inhibit adhesion molecule expression (e.g. VCAM-1, ICAM-1 and ELAM-1) and TNF-α-induced NF-κB activation. The study demonstrated the emodin has the ability to block P2X7R (purinergic receptor) and thus antagonize the ATP to stimulate IL-1β release and hinder phagocytosis. These abilities of emodin counteract the local and systemic effects pancreatitis	[106]
7.	Hesperidin Derived from: Citrus fruits	Cerulein-provoked AP in animal model	Hesperidin reduced intensity of the inflammatory process and the severity of the disease (indicated by amylase level) and the NO and ROS generation (as confirmed by chemiluminescence studies)	[107]
8.	Lignan – Nordihydroguaiaretic acid (NDGA) Derived from: Creosote bush		NDGA prevents acinar cells necrosis and promotes apoptosis by enhancing Bcl-2 expression by encouraging PP2A phosphorylation and procaspase-3 to caspase-3 conversion. It also augmented various heat shock proteins expression (HSPD1, DNAJ C15 and HSP 27) hindering the AP development. It blocked the NF-κB pathway by both decreased expression and activation by phosphorylation of p38) and also lowered the ROS level and strengthened antioxidative mechanisms (increased GSH and SOD)	[108]
9.	Ligustrazine Derived from: *Ligusticum wallichii*	AP rat models	Ligustrazine reduced the levels of TNF-α, IL-6, IL-1β, pancreatic MPO activity, amylase and degree of infiltration of inflammatory cell in pancreas, thereby reducing AP	[109]
10.	Resveratrol Metabolite: Dihydroresveratrol Derived from: Grapes, blueberries, peanuts, pistachios, soy, and *Polygonum cuspidatum* beans.	Rats with AP Animal models (cerulein, sodium taurocholate and CCK-8-induced AP)	Resveratrol induced PACs apoptosis by the upregulation of FasL gene expression. Resveratrol and its metabolite dihydroresveratrol protect animals against AP by mechanisms based on the downregulation of proapoptotic caspase-3, Bax and upregulation of antiapoptotic Bcl-2 Resveratrol and its metabolite dihydroresveratrol exerted anti-inflammatory effect through NF-κB inhibition and decreased TNF-alpha, IL-6, IL-1β and IL-8 expression in the pancreas thus reducing the effects of AP	[110,111]
11.	Rhein Derived from: *Rheum* spp., *Senna* spp.	*In-vitro* rat pancreatic acinar cells Experimental AP animal models	Rhein promoted dose-dependent enhancement of the ratio of apoptotic-to necrotic cells, the level of cytochrome C, caspase-3, p53 and Bax/Bcl-2 ratio indicating the ability to channel the mitochondrial apoptosis of injured cells rather than necrosis thus reducing the effects of AP Conjugated HPDM-rhein compound reduced the AP severity which was indicated by lower amylase, lower levels of IL-6 and TNF-α in plasma, lung and pancreas	[112,113]
12.	Rutin Metabolite: 3,4-Dihydroxytoluene Derived from: Citrus fruits, black tea, apple, grapes.	RAW264.7 macrophage-LPS stimulated inflammatory conditions AP L-arginine induced AP model AP and CP models	3,4-Dihydroxytoluene exerted anti-inflammatory by deactivating NF-κB signalling Rutin decreased the pancreatic injury indicated by less necrosis, infiltration, oedema, and lower serum levels of the pancreatic enzymes and also increased apoptosis Rutin reduced inflammation via several mechanisms such as decreased expression of various cytokines like TNF-α, IL-1β, IL-6 and decreased neutrophil infiltration	[114–116]

AP, acute pancreatitis; PACs, pancreatic acinar cells; ROS, reactive oxygen species; SAP, severe acute pancreatitis; SOD, superoxide dismutase.

treatment, were also being investigated. Food items fortified with clinically accepted phytochemicals with pancreato-protective or pancreato-regenerative properties would also serve as an attractive therapy for patients with AP.

Stem cell and other cellular therapies

Recent studies employing stem cells for treating AP are widely described. Effectively, MSCs have been used in various fields such as the autoimmune disease, tissue engineering and gene delivery vehicle because of their potential for self-renewal, immunosuppression, differentiation, paracrine signalling and cellular migration.[50] Also, MSCs can be isolated from multiple organs and tissues and they are also of low immunogenicity. Without having effective therapeutic options, these stem cells have been used for treating acute inflammation and wound injury, as they engraft into pancreatic wounds and scars contributing to the remodelling of injured tissues. Studies showed that the MSCs attenuate inflammation via their immunomodulatory effects by suppressing pro-inflammatory cytokines, secreting anti-inflammatory cytokines and cellular growth factors to promote angiogenesis, regulating immune cell activation and decreasing the apoptosis of PACs.[51,52]

Like MSCs, bone marrow-derived stem cells (BMSCs) were investigated for their potential to treat SAP. A study demonstrated the use of micro-RNA-9 (miR-9) modified BMSCs (pri-miR-9-BMSCs) in AP that significantly reduced infiltration, pancreatic oedema, the release of lipase and amylase, necrosis and also decreased local/systemic inflammatory response. These productive effects were indicated by reduced levels of TNF-α, IL-6, IL-1β, MPO, HMGB1, CD68 and increased levels of IL-10, IL-4 and TGF-β. miR-9 is negatively correlated with AP, and when it is delivered by BMSCs to injured pancreas or PBMC (peripheral blood mononuclear cells), it can target the NF-κB1/p50 gene inhibiting the NF-κB signalling pathway (IκBα↑, NF-κB1/p50↓, IκBβ↑).[53]

Umbilical cord-derived mesenchymal stem cells (UCMSCs) were studied for their effect on SAP, and it was found that the UCMSC injection at diseased site reduced pancreatic tissue damage, ameliorated inflammation, oedema, and necrosis and reduced the serum levels of lipase and amylase. UCMSCs also reduced PACs apoptosis and pro-inflammatory cytokines (IFN-γ, TNF-α, IL-6, and IL-1β) in serum, while increasing anti-inflammatory cytokines (IL-4 and IL-10) level. Another study was attempted in which the UCMSCs were transfected with angiopoietin-1 (ANGPT1), a key factor associated with regulation of angiogenesis, endothelial cell survival and vascular stabilization. Angiopoietin-1 overexpression reduced both PAC injury and pro-inflammatory cytokines at serum and promoted angiogenesis.[54,55]

In another study, human mesenchymal stem cells (hMSCs) were intravenously administered along with the TSG-6 expression to treat SAP. The results showed that the increase of oxidative stress, NLRP3 inflammasome activation and NF-κB signalling were inhibited following administration, which dependent on the presence of acinar cell CD-44 receptors. In non-infectious inflammation, hMSCs were able to interact with inflammatory or immune cells and produced soluble cytokines such as TSG-6, prostaglandin (PG)E2, IL-10, transforming growth factor (TGF)-β, IL-4, IL-1 receptor antagonist, hepatocyte growth factor, indoleamine 2,3-dioxygenase, inducible NO synthase, human leucocyte antigen (HLA)-G64 and galectin-1 and reduced inflammation.[56]

Bone marrow-derived mesenchymal stromal cells (BM-MSCs) were administered as a therapy for SAP, and the results showed that the BM-MSCs administration increased antioxidant activity such as glutathione peroxidase (GPx) and superoxide dismutase (SOD).[57,58] BM-MSCs also enhanced neovascularization and angiogenesis. Also, BM-MSCs when pretreated with stromal-cell-derived factor 1α (SDF-1α) increased angiogenesis indicated by the expression of angiogenesis markers (VEGF, CD31 and vWF) in the pancreatic tissues. In another study, MSC transplantation along with granulocyte colony stimulation factor (G-CSF) enhanced the proliferation of transplanted BM-MSCs by binding to G-CSF receptors which promoted BM-MSC homing and enhanced the BM-MSCs ability to differentiate pancreatic lineage cells indicated by the pancreatic marker expression (Nkx6, Ngn3 and Pax4). These studies revealed the potential of MSCs in the treatment of AP.[59]

Although the results of MSC therapies are very promising in animal studies, these approaches are not translated into clinical trials till date. The major reasons are the risk of rejetion and the ethical concerns associated with allogenic cell therapy. When using the MSC therapies combined with immune-modulating drugs for treatment, the dosage of drugs is particularly important, which is directly affects the degree of drug-dependent immune response. As in the case of AP, when a therapy is said to be effective if only it does not completely inhibit the immune response while being able to reducing the body's excessive inflammation. Also, the specific indicators or biomarkers to be refined and identified that are easy to monitor in the clinical trials.

Immune cell-based therapy is also investigated for treating AP. A study involving the transfer of hemin-activated macrophages in AP-induced mice showed protection against early and late stages of experimental AP.[60] The elevated expression of haem oxygenase-1 in haem-activated macrophages promotes the production of anti-inflammatory agents namely carbon monoxide and biliverdin, which

induce IL-22, p38 MAPK and IL-10.[53,61] In another study, IL-4 and IL-13 were investigated for their ability to aid in the conversion of pancreatitis-activated M1 peritoneal macrophages to reparative M2 macrophages. But the cytokines tend to degrade and lost their activity *in vivo*.[62] This immune cell-based therapy needs more experimental study to successfully implement in the treatment approach for AP.

Nanotechnology and targeted delivery in AP

Nanotechnology deals with the particles of nanomolecular range that can be used in various therapeutic and biomedical applications. It is employed for favourable physicochemical properties as well as in targeted delivery of the molecule. These nano altered physicochemical properties increase the efficacy of the various therapeutic methods. Some of the interesting and recent nanotechnological approaches to treat AP are discussed below.

Macrophages are divided into M1 and M2 macrophage, and they play a major role in various inflammatory disorders. M1 macrophages secrete pro-inflammatory cytokines, whereas the M2 macrophages secrete anti-inflammatory cytokines. Hence, in the acute inflammatory disorders, the healing process can be induced by shifting M1 macrophages production to M2 macrophages. Previous studies indicate that when treating the macrophages with carbon monoxide (CO), there was an increased secretion of anti-inflammatory cytokines and inhibition of pro-inflammatory cytokines indicating that the CO has the ability to modulate the production of M2 macrophages. In a study, nanotechnology-based CO donor in the form of CO-bound haemoglobin vesicle (CO-HbV) was used to evaluate the therapeutic efficiency of CO-HbV in secondary distal organ-injured model mice fed with a choline-deficient ethionine-supplemented diet. The CO-HbV treatment suppressed AP by inhibition of systemic pro-inflammatory cytokine production, oxidative injuries in pancreatic tissue and neutrophil infiltration. Also, this treatment diminished the damage to other distal organs such as lungs, liver and kidneys owing to the neutrophil infiltration suppression. This study proved the protective effect of CO-HbV in AP-induced multiorgan damage.[63,64]

In another study, two-generation 5 (G5) polyamidoamine (PAMAM) dendrimers with distinct surface groups G5-OH and G4.5-COOH were investigated for their potential to treat pancreatic injury in caerulein-induced mouse model of AP. Both the dendrimers significantly reduced inflammatory infiltration of macrophages into the pancreatic tissues thereby decreasing the pathological changes in pancreas. Also, they inhibited the expression of pro-inflammatory cytokines in AP mice as well as in LPS induced inflammation of mouse peritoneal macrophages *in vitro*. G5-OH also produced significant reduction in the total monocytes and plasma white blood cells (WBCs) number in AP mice, and its mechanism for anti-inflammatory reaction pertained to the inhibition of NF-κB nuclear translocation in macrophages.[65]

Apart from these, a study was performed in which the macrophages depletion via clodronate liposomes injection protected against caerulein-induced pancreatitis in mice.[66] Also, nanotechnology is being investigated for the targeted delivery of phytoceuticals. Currently, there are no evidences for the effective use of nanotechnology in treating AP but there are lots of studies stating the use of nanotechnology for the targeted delivery of phytoceuticals in efficient treatment of various cancers. Soon, nanotechnology will also be employed in the delivery of phytoceuticals for treating AP.

Improvements in current clinical approaches

The SAP is one of the severe forms of pancreatitis which leads to increased morbidity and mortality. The SAP is clinically manifested as the severe inflammatory response syndrome followed by multiple organ dysfunction. The management of SAP varies depending on the severity and the type of disease manifestation.[67] Conventionally, the nothing by mouth strategy is used as a palliative clinical care to reduce the bowel load in order to resolve the pain and normalize the excess pancreatic enzymes.[68] This strategy is based on the fact that the gut microflora is translocated and overgrown in case of infectious necrotizing pancreatitis due to the disturbance in the intestinal motility and increased mucosal permeability and atrophy.[69] Since there are no specific pharmacological therapies for AP, the improvement in the current AP management strategies for reducing the morbidity are derived from the various randomized clinical trials and preclinical studies are enlisted in Table 1. Also, the nutritional intervention is an integral part of clinical management in AP patients. Diet and nutritional supplements are proven to be critical in restoring the energy balance, maintaining the gut barrier function and providing immunomodulatory and antioxidant effects.

The major cause of mortality in AP patients is due to the imbalanced inflammatory response in the body. So, immunomodulation is considered to an important strategy to improve the prognosis of SAP patients. The currently available immunomodulatory therapy focuses on regulating the maturation and apoptosis of immune cells. In addition, the use of MSCs and multidrug combination therapy also provides new potential theragnostic interventions. Yet, the

challenges in the SAP immunomodulatory therapy need to be emphasized. The use of anti-inflammatory drugs or therapies down-regulates the immune response from the onset of AP. However, when CARS and intestinal bacterial translocation occur, stimulation and enhancement of the immune response may defy the therapeutic effects of the anti-inflammatory drugs. Furthermore, the specific timing of medication should also be combined with individual indicators of patients, such as the number of immune cells in peripheral blood, expression level of anti-inflammatory and pro-inflammatory factors, etc. For instance, the cytokines are abundantly secreted in the initial hours of tissue insult, the anticytokine therapies especially TNFα may work effectively when given in the appropriate therapeutic window. Hence, the time and dosage of personalized SAP therapies need to be refined for the clinical trials as the therapeutic window may differ depending on the individual's immune system responses.

Bench to bedside

As a rapidly progressive condition, the severity of AP can change quickly within an extremely short amount of time. The current management of AP usually consists of combined treatments of nutritional support, analgesics and protease inhibitors. Unfortunately, these therapies exhibit limited efficacy due to their lack of specificity and timing.[70] Therefore, novel diagnostic and therapeutic approaches for AP are the need of the hour. In human pancreatitis, the patient dies early as most of the organ failures occur before initiation of treatment. It has also been observed that the novel agents that attenuates experimental AP are less effective when administered in human trials several hours or days after the onset of disease.[71] There is also the need to use widely accepted prognostic markers to determine the disease severity and to select the inclusion criteria and interpretable end points in a clinical trial.

It is also observed that the combinatorial treatment is more effective in AP as satisfactory therapeutic effect is not achieved through a single treatment/intervention. Reports suggest that when rats with SAP are treated with dexamethasone or N-acetylcysteine alone, the injury of pancreas reduces, but the level of IL-6 in blood and the lung injury remains elevated.[72] But the combined use of N-acetylcysteine and PECAM-1 was effective in alleviating the severity of SAP and related organ damage, and the effect was better than that of single use.[73] In addition to the combinatorial approaches, it is important to remember that SAP is an alternating process between SIRS and CARS. Therefore, both anti-inflammatory drugs and immunomodulatory agents should be used for management of SAP.

Recent trends in nutrition towards AP treatment

Probiotics

Probiotics are live microbes which when consumed in adequate amounts provides various beneficial health effects. Probiotics can also be recommended with prebiotics or synbiotics which itself does not have any nutritional value but are added to enhance the activity of probiotics. In case of AP pathogenesis, probiotics have been suggested to reduce the gut bacterial translocation by acting on different levels of host–bacterial interactions; the intestinal lumen, the intestinal epithelium and the immune system.[74] Also, the probiotics and prebiotics are shown to reduce the necrotic tissue infection in SAP and restore the intestinal barrier homeostasis in animal models and primary clinical trials. Some examples of such probiotics include single strain probiotic *Lactobacillus plantarum* when consumed along with oat fibre with a dosage of 109 × 2/daily dose reduces the pancreatic infection.[75,76] The multistrain probiotic which contains high diversity of probiotic bacteria of dosage up to 40 × 109/daily dose reduce the severity of systemic inflammatory response syndrome (SIRS) which in turn significantly reduces the risk of multiorgan dysfunction syndrome (MODS).[77]

Glutamine supplements

More recently, studies suggest that glutamine supplements reduce the endotoxin levels in plasma by decreasing the gut permeability and help in improving the gut barrier function in patients suffering from SAP. When taken in combination with normal saline and hydroxyethyl starch in resuscitation fluids, glutamine was more efficient in relieving inflammation and sustaining the intestinal barrier in patients with severe AP.[78]

Dietary polyunsaturated fatty acids

Dietary polyunsaturated fatty acids are primarily known for its immunomodulatory and other beneficial health-promoting effects. Wang *et al.*[79] reported a comparison of diet containing different lipid compositions of soybean oil and/or fish oil-based fat solutions in a randomized double-blind clinical trial involving 40 SAP patients. This study reported that patients consuming diet supplemented with ω−3 FAs increased the levels of eicosapentaenoic acids and decreased the pro-inflammatory cytokine expression. Also, it improved the pulmonary function, reduced the continuous renal replacement therapy duration and further it attenuated the inflammatory response of the pancreas. An

increased *n*−3 PUFA tissue status in the pancreas decreases the systemic inflammatory response in AP and reduce fibrotic changes in chronic pancreatitis.[80,81]

Vitamins

Vitamins are previously reported to have antioxidant activity and also shown to be inversely associated with AP. On the other hand, oxidative stress plays an important role in AP pathogenesis by inducing the systemic inflammatory responses.[82–84] The other factors like glutathione depletion, xanthine oxidase activation and thiol oxidation in proteins are critical features of the pancreatic disorders.[85–87] Accordingly, plasma concentrations of vitamins A and C were found to be very low in AP patients when compared to healthy controls.[88–91] Recently, it is reported that vitamin D supplementation attenuates gallstone-related AP.[92] Vitamin supplementation assessed in combination with other antioxidants or in vitamin-only therapy has been evaluated earlier and yielded mixed outcomes. Yet, menadione (vitamin K) exhibits an anti-inflammatory effect by down-regulating substance-P and H_2S signalling via the NF-κB pathway.[93] Menadione also has other possible effects like apoptosis of injured PACs.[94]

Conclusion

Based on current literature, it is clear that there is a need for more specific pharmacological therapeutic measures for treatment of AP. Besides the fact that AP also causes lung injury and distant organ failure if left untreated, recurrent AP increases the risk for pancreatic adenocarcinoma.[95] In most of the AP cases, the disease is caused by the obstruction of gallstones and the sustained biliary stone entrapment or sludge blockage possibly increases the disease severity.[96] Current clinical and surgical treatments bring a short-term relief by providing palliative care but the root cause is left untreated. Hence, the high risk for recurrent episodes of AP in patients remains a challenge. Thus, from the current literature, there is a high demand for nutrition-based prevention and treatment strategies for AP and other pancreatic diseases in general which may pharmacology inhibit the progression of AP to its severe forms.

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