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REVIEW

Experimental and clinical evidence of antioxidant therapy in acute pancreatitis

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Abstract

Oxidative stress has been shown to play an important role in the pathogenesis of acute pancreatitis (AP). Antioxidants, alone or in combination with conventional therapy, should improve oxidative-stress-induced organ damage and therefore accelerate the rate of recovery. In recent years, substantial amounts of data about the efficiency of antioxidants against oxidative damage have been obtained from experiments with rodents. Some of these antioxidants have been found beneficial in the treatment of AP in humans; however, at present there is insufficient clinical data to support the benefits of antioxidants, alone or in combination with conventional therapy, in the management of AP in humans. Conflicting results obtained from experimental animals and humans may represent distinct pathophysiological mechanisms mediating tissue injury in different species. Further detailed studies should be done to clarify the exact mechanisms of tissue injury in human AP. Herein I tried to review the existing experimental and clinical studies on AP in order to determine the efficiency of antioxidants. The use of antioxidant enriched nutrition is a potential direction of clinical research in AP given the lack of clues about the efficiency and safety of antioxidant usage in patients with AP.

Key words: Acute pancreatitis; Antioxidants; Clinical; Experimental; Oxidative stress

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INTRODUCTION

Acute pancreatitis (AP) can present as a wide clinical spectrum ranging from a mild, self-limiting localized disease to fatal widespread multi-organ failure with high mortality rates. Mild pancreatitis is the inflammation and edema of the pancreas, with additional features of necrosis and secondary injury to extrapancreatic organs in severe pancreatitis[1-3]. AP is characterized by acute inflammation and necrosis of pancreatic parenchyma, necrosis of pancreatic fat, hemorrhage, and inflammatory infiltration[4]. Since pancreatic cell death occurs according to either necrosis or apoptosis mechanisms, many necrotic and apoptotic cells can be seen within pancreas parenchyma. The study of Booth *et al*[5] found that oxygen free radical (OFR) induction in acinar cells promoted apoptosis whereas inhibition of OFR generation led to an increase in necrosis accompanied by reduced ATP. These findings suggest that OFR generation within acinar cells may be a protective response during pancreatitis. The main reason for necrotic or apoptotic cell death is the early activation of pancreas zymogens, especially cathepsin and trypsinogen inside the pancreas. Scott *et al*[6] showed that excessive OFR in

a pathologic state can cause tissue and cell damage. The OFR participates in the pancreas edema process in AP, and may participate in the pancreas necrosis process. Furthermore, OFR are involved in the generation of pain as another important clinical feature of patients suffering from AP[7]. The OFR, as highly reactive species, directly attacks lipids and proteins in the biological membranes and thus disrupts their functions. The action of OFR includes oxidation of lipids in the pancreatic cell membrane and oxidatively modified proteins, depolarization of the mitochondrial membrane, and induction of DNA fragmentation[8].

Aerobic organisms require ground state oxygen to live; however, the use of oxygen during normal metabolism produces OFR[9,10]. OFR are required for the maintenance of tissue homeostasis. Physiologic levels of OFR can regulate transcription, serve as signal molecules and defend against pathogen infections[11]. The mitochondria, endoplasmic reticulum, cytosol, and nuclear membranes have all been shown to be sources of OFR[12]. The primary function of the electron transport chain located in the inner mitochondrial membrane is ATP synthesis via oxidative phosporylation[13]. The superoxide radical formed during cellular metabolism is mainly produced during electron transport in the mitochondria and is released to both the mitochondrial matrix and intermembrane space[9,10,14,15]. Superoxide, depending on its location, causes potential oxidative damage to different proteins and lipids, as well as DNA[16]. The end product of the respiratory chain is water generated in a four-electron reduction of molecular oxygen. However, a small portion of oxygen is involved in the generation of OFR, including superoxide anion radicals, hydrogen peroxide, hypochlorous acid, and the extremely reactive hydroxyl radical[10,17]. These free radicals, each containing an unpaired electron, are energetically unstable and highly reactive. OFR can attack the double bonds of unsaturated phospholipids in cell membranes, which eventually degrade the structural integrity of cell membranes. Lipid oxidation can lead to the loss of the integrity of both plasma membrane and intracellular membranes, such as that of lysozomes and the endoplasmic reticulum, which then leads to an intracellular leak of proteases or an influx of Ca2+ resulting in necrosis[18]. OFR also impairs the functions of enzymes by causing fragmentation of polypeptide chains or cross-linking sulfhydryl groups in proteins. In addition, they cause strand breaks or abnormal cross-linking in DNA[19-21]. Damage to DNA may lead to a DNA-damage response, including activation of p53 and poly-ADP ribose polymerase (PARP) (a nuclear enzyme). While activation of p53 causes apoptosis and cell cycle arrest, hyperactivation of PARP leads to necrosis[22]. The hydroxyl radical is the most reactive species and can attack and damage almost all molecules found in the living cell. Being so reactive, it attacks DNA, a free radical chain reaction cascades through the DNA and causes chemical alterations of the bases as well as strand breakage. The best characterized biological damage caused by hydroxyl radicals may be their ability to stimulate the free radical chain reaction known as lipid peroxidation[12,23]. One hydroxyl radical can result in conversion of many hundred fatty acid chains into lipid hydroperoxides. Accumulation of lipid hydroperoxides in a membrane disrupts its functioning. Some of the products of lipid peroxidation, malonaldehyde (MDA) and 4-hydroxynonenal, increase the permeability and deformability of the membranes in which they are found. Mitochondrial membranes are particularly susceptible to this sort of damage, perhaps because they combine a high risk of OFR-mediated peroxidation[12]. We have shown mitochondrial degeneration within pancreatic acinar cells in experimental pancreatitis[1,24].

OFR indirectly act on the arachidonic acid cascade by increasing the production of thromboxane, which lowers tissue circulation by its potent platelet-aggregating and vasoconstricting effects[25]. Additionally, OFR enhance the production of leukotriene B4 which promotes activation of leukocytes and discharge of lysosomal enzymes[26]. As a secondary effect, polymorphonuclear leukocytes are responsible for the respiratory burst that leads to an enhanced production of radical species and activated enzymes and further cell damage[27]. The results of Rau *et al*[28] indicate that OFR play an important mediator function in early and later courses of AP. Their findings suggest that OFR species are important mediators but not necessarily triggers of tissue damage in AP. The degree of oxidant-antioxidant balance changes in the early phase of human AP, correlating with the clinical severity of pancreatitis[29]. Park *et al*[30] reported higher plasma levels of lipid peroxides and myeloperoxides and lower superoxide dismutase (SOD) activity in patients with severe AP than in those with mild AP. OFR may thus be closely associated with the inflammatory process and the severity of AP. Thareja *et al*[31] reported that high oxidative stress was observed during the early phase of AP and that gradually improving antioxidant status was associated with a better clinical outcome in patients with AP. The concentration of plasma lipid peroxides is a particularly meaningful index for determining the severity of the disease in humans[30,32].

During the later stages of AP, the major pathophysiological role seems to be the attraction and activation of leukocytes, which in turn contribute to enhanced radical generation and acinar cell damage[33,34]. Oxidative stress in the neutrophils (activated during the inflammatory response to acinar injury) may be responsible for further propagation of local and systemic inflammation[5]. Synergy between pro-inflammatory cytokines and oxidative stress occurs in the development of the inflammatory response in AP[35]. Proinflammatory cytokines such as interleukin (IL)-1, 6 and tumor necrosis factor (TNF) and microvascular ischemia are also important factors in the pathophysiology of AP[33,34]. Serum levels of proinflammatory cytokines, such as TNF-alpha and IL-1beta, increase during the course of AP and appear to be the driving force for the initiation and propagation of

the systemic response. Accordingly, pretreatment with either an antibody against TNF-alpha or a blockade of TNF-alpha production with pentoxifylline ameliorates experimental AP[36]. A cross-talk between oxidative stress and proinflammatory cytokines, particularly TNF-alpha amplifies the inflammatory cascade through different mechanisms, such as the activation of mitogen activated protein kinases and nuclear factor-kappa B (NF-κB) and/or the inactivation of protein phosphatases[35,37-39].

In addition to increased levels of plasma and tissue lipid peroxides, decreased levels of plasma antioxidants such as vitamin A, vitamin C[40], vitamin E[41], selenium[42], β carotene, whole-blood glutathione, and the activity of plasma glutathione peroxidase[21] have been found in patients with AP. Moreover, lower levels of selenium in toenails of AP patients and lower selenium concentrations in red blood cells of patients with severe AP have been detected[40].

Since experimental[42,43] and clinical studies[31,44] have provided some support for the concept that oxidative stress is the common pathway for the pathogenesis of AP, one reasonable idea is to use antioxidant regimens in the management of AP to complement its traditional therapy. In fact elucidation of all of the mechanisms above mentioned and their interactions is critical in developing a treatment based on the pathophysiology of AP. However, clinical evidence showed that antioxidant administration to patients with AP was not as beneficial as the antioxidant administration to experimental animals. Perhaps the key steps in the pathogenesis of AP are not yet fully understood. It is not possible to clearly determine whether oxidative stress is a cause or an effect of AP. This review highlights the experimental and clinical evidence of the benefit of various antioxidants in AP.

ANTIOXIDANT THERAPY IN AP

Antioxidants may function to prevent the formation of, or to detoxify, free radicals or to scavenge OFR. Halliwell[45] has proposed this useful definition, "an antioxidant is any substance that, when present at low concentrations compared to those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate". In experimental pancreatitis, the beneficial effects of antioxidants may be associated with the inhibition of NF-κB activity[46]. Types of antioxidants include antioxidant vitamins (e.g., ascorbic acid, α tocopherol, β-carotene), inorganic antioxidants (e.g., selenium), synthetic antioxidants (e.g., butylated hydroxyanisole), and a range of plant-derived polyphenols[47]. Organisms widely use glutathione peroxidase, glutathione transferase, SOD, catalase (CAT), and a variety of other antioxidants to protect themselves against generation of OFR[48-50]. Some authors have studied the effects of various antioxidants in experimental animals and patients with AP. They used both natural and synthetic antioxidants in order to protect the pancreas from deleterious effects of OFR. The following sections summarize data obtained from experimental and clinical studies about the efficacy of some oxidants in AP.

Alpha tocopherol

Tocopherols belong to a class of phenolic antioxidants which can inhibit lipid auto-oxidation by scavenging free radicals and by reacting with singlet oxygen. The vitamin E activity of alpha-tocopherol may be attributed to its efficient inhibition of *in vivo* lipid oxidation[51]. Fat-soluble antioxidants act directly in the lipid bilayer of plasma and cell membranes by interacting with membrane lipophilic components. A natural antioxidant, alpha-tocopherol has been found to be beneficial in inhibiting intermolecular connections of lipid peroxides in liver of dogs with AP[52]. Vitamin E, including tocopherols and tocotrienols, is a fat-soluble antioxidant. To my knowledge the effect of vitamin E on AP has not been studied. Since they accumulate within tissues, fat-soluble substances have high toxic risk thereby limiting their clinicical application and widespread utilization. The results of combined therapies, including vitamin E, will be discussed below.

Ascorbic acid

Ascorbic acid functions in multiple, complex ways, acting as a hydrogen donor, a metal inactivator, and a peroxide destroyer[31]. The study of Bonham *et al*[53] demonstrated that plasma ascorbic acid concentration was significantly below normal in patients with early phase AP; however, Sajewicz *et al*[32] reported that patients with AP had double the plasma ascorbic acid values than healthy volunteers. Few studies have investigated the therapeutic efficacy of ascorbic acid in experimental animals with AP whereas many have examined its effects singly or within an antioxidant mixture in patients with AP. Two decades ago, Nonaka *et al*[54] reported that CV3611, a synthetic free radical scavenger prepared from ascorbic acid, had an important therapeutic effect on the development of AP in mice. However since then, another experimental or clinical study evaluating the benefit of this agent in AP has not been performed. Du *et al*[55] have reported that high dose vitamin C has a therapeutic effect in humans with AP. Their results indicate that vitamin C decreases hospitalization and duration of disease, and increases the cure rate by blocking lipid peroxidation, diminishing proinflammatory cytokines, and improving cellular immune function. The results of combination therapies will be discussed below.

Beta-carotene

Beta-carotene protects lipids by interfering with photosensitized oxidation, and behaves as a reducing agent by trapping radicals. In addition to its singlet oxygen-quenching properties, beta-carotene has good radical-trapping properties at low partial pressures of oxygen, a condition which prevails in healthy tissues. In biological systems, alpha-tocopherol and beta-carotene exhibit synergism by mutually reinforcing their respective activities.

Synergism also takes place in a cascade where ascorbic acid can be regenerated at the expense of more oxidizable substrates[51]. In patients with mild AP, the concentrations of beta-carotene at final review has been found significantly higher than those in patients with severe AP[56]. The correlation between low antioxidant level and high severity of disease suggests the utility of antioxidant supplementation therapies. Lavy *et al*[57] have reported some possible protective effects of treatment with beta carotene in regards to the severity of post-endoscopic retrograde cholangiopancreatography pancreatitis (ERCP). In a double-blind trial, 321 patients were given a single dose of natural beta carotene. The rate of severe pancreatitis was found to be lower in the beta carotene-treated group. Adverse events were not reported.

Caffeic acid phenethyl ester

Caffeic acid phenethyl ester (CAPE) is a phenolic compound and an active substrate of propolis. Several investigators have shown that CAPE acts as an anti-inflammatory by inhibiting the release of arachidonic acid from cell membranes, and suppressing cyclooxygenase (COX)-1 and COX-2 enzyme activities[58], and reducing antioxidant activity by lipoxygenase inhibition[59,60]. Buyukberber *et al*[46] have found CAPE to be benefical in improving the biochemical and histopathological findings in cerulein-induced AP in rats. Turkyilmaz *et al*[61] have also reported the beneficial effect of CAPE on acute necrotizing pancreatitis in rats. To my knowledge, no clinical data has been reported about the effect of CAPE on AP in humans. The data obtained from experimental animals are promising. CAPE has been shown to inhibit the production of proinflammatory cytokines by inhibiting nuclear transcription factor activity[62].

Carnitine

As an antioxidant, acetyl l-carnitine culminate most probably protects tissues from oxidative stress by stabilizing cell membranes, rendering them more resistant to free radicals, perhaps by facilitating the repair of the phospholipid bilayer damaged by oxidant stress, rather than acting as a direct scavenger of free radicals or decreasing their generation[63]. Data so far obtained would suggest that prior administration of acetyl l-carnitine ahead of caerulein challenge has proven protective efficacy that could possibly be ascribed, in part, to its regulation of the oxidant/antioxidant balance and modulation of nitric oxide (NO) release and myeloperoxidase activity that may ultimately lead to regulation of the inflammatory events associated with AP[64].

Green tea

Another naturally occurring antioxidant comes from the caffeine-free extract from leaves of green tea (Camellia sinensis), shown to reduce the degree of AP and attenuate the activation of the transcription factor NF-κB, as well as the formation of proinflammatory cytokines[65]. It also significantly decreases lipid peroxidation[65,66] and the formation of nitrogen-derived radicals in rodents[65].

Melatonin

Melatonin, the hormone produced mainly by the pineal gland, has been studied widely. Both *in vitro* and *in vivo* studies have identified melatonin as a potent scavenger of highly toxic hydroxyl radical and other oxygen-based radicals. Potent anti-inflammatory effects of melatonin may be related to a reduction of the inflammatory mediators produced during the inflammatory process[67]. Several experimental studies showed that melatonin is effective in reducing oxidative stress-mediated AP in rodents[68,69]. Recently, we reported a potent therapeutic effect of melatonin on caerulein-induced AP and associated liver injury[1]. We also demonstrated its potent effect on the protection of cell ultrastructure[43]. Melatonin decreases tissue MDA levels and increases antioxidant enzyme levels or activities[1,3,43]. Melatonin treatment was found to promote the spontaneous regeneration process of pancreatic tissue in rats[69]. Jaworek *et al*[70] have reported that pinealcetomy aggravates AP in the rat. Interestingly, Belyaev *et al*[71] presented the dynamic changes of endogenous melatonin in the early phase of human AP. Melatonin concentrations during the first 24 h after the onset of pain in younger patients (< 35 years) were significantly higher than levels in older patients (> 35 years). They concluded that high endogenous serum melatonin levels in the first 24 h after the onset of AP played a protective role and favoured a mild disease course in humans, especially in young patients. Another clinical study performed by Chen *et al*[72] indicates that delayed neutrophil apoptosis is associated with mild and severe AP in humans. Neutrophil apoptosis plays a critical role in minimizing the autodestructive potential of neutrophils. The data from the study show that melatonin promotes neutrophil apoptosis in human AP. Melatonin administration is promising for the treatment of AP in humans. However, further studies are still needed.

N-acetyl-cysteine

N-acetyl-cysteine (NAC) is a thiol compound which, by providing sulphydryl groups, can act both as a precursor of reduced glutathione and as a direct free scavenger, hence regulating the redox status in the cells. In this way, it can interfere with several signaling pathways that play a role in regulating apoptosis, angiogenesis, cell growth and arrest, and inflammatory response[73]. NAC has been found to be hugely effective in reducing oxidative stress-induced pancreatic injury in rats[74,75] by enhancing the ability of acinar cells to produce IL-10[74], preventing the impairment of Ca^{2+}[75], and downregulating the expression of chemokines, monocyte chemotactic protein-1, and macrophage inflammatory protein-2[76]. Moreover extrapancreatic complications (liver and lung injury) during AP induced by bile-pancreatic duct obstruction were palliated by NAC treatment[77]. Onur *et al*[78] have reported that NAC, especially combined with hyperbaric oxygen, decreases oxidative stress parameters, serum amylase, cal-

cium, and lactate dehydrogenase levels, as well as the histopathological score. To our knowledge, only one study shows the effects of NAC in patients with AP. Recently, Milewski *et al*[79] investigated the effects of NAC (administered by intravenous or oral route) on post-ERCP. Regretfully, NAC failed to demonstrate any significant preventive effect on post-ERCP pancreatitis or on serum and urine amylase activity. The results of combination therapies, including NAC, will be discussed below.

Resveratrol

Alcoholic AP predominates in countries where other forms of alcoholic drinks rather than wine are preferred. Presumably, wine contains factors that protect the pancreas against alcohol-induced AP. One of these factors may be resveratrol. Resveratrol, a naturally occurring antioxidant, acts as a free radical scavenger[80], but to date, no clinical study has been performed on antioxidant and free radical scavenger potentials of resveratrol on AP. Resveratrol has been found beneficial in AP in rats[81-83]. Lawinski *et al*[84] found stilbene derivatives (resveratrol and diethylstilbestrol) effective in preventing pancreatic cells from structural changes to OOH-induced AP in Wistar albino rats. Resveratrol and diethylstilbestrol protect the pancreas against prooxidative activity of hydroperoxide; stilbene derivatives significantly inhibit the free radical generating reactions. Leonard *et al*[85] have demonstrated that resveratrol can clear hydroxyl, superoxide, and metal inductive radicals. Kimura *et al*[86] have found that resveratrol inhibits lipoxygenase, an enzyme that is converted into powerful inflammatory and white cell stimulating agents known as leukotrienes, hepoxillins, and lipoxins through arachidonic acid. Resveratrol may exert its therapeutic effect on severe AP by lowering pancreatic OFR and reducing pancreatic tissue infiltration of neutrophils[87]. Due to its strong effect of inhibiting activation of NF-κB and reducing secondary activation of cytokines, resveratrol is regarded as a promising drug for blocking the initiation and progress of AP. Though no document as yet illustrates the function of resveratrol in AP in humans, primary trials have found that resveratrol could inhibit the production of TNF and IL-6 in pancreatitis. More research is required[87]. An increasing amount of data has confirmed that resveratrol could relieve the pathologic injury of the pancreas and extra-pancreatic organs (intestines, brain, lungs, *etc*.) induced by severe AP[88-90]. Further clinical studies are needed.

Quercetin

Quercetin is a naturally occurring plant flavonoid abundantly present in onions, fruits, and Chinese herbs. Several studies pointed out the beneficial biological activities of quercetin which include antioxidant, antiinflammatory, antiatherosclerotic, and anti-tumor properties[91-93]. The study of Carvalho *et al*[94] has demonstrated that the flavonoid quercetin attenuates the severity of cerulein-induced AP in mice. In particular, they reported that quercetin treatment reduces pancreatic inflammation and associated tissue injury through suppression of neutrophil infiltration, TNF-alpha, IL-1β and IL-6 cytokine production, and TNF-alpha expression, and increased IL-10 cytokine production. Since high oral and subcutaneous doses of quercetin did not manifest any clinical signs of toxicity, it may be safe and nontoxic in the treatment of AP; however, further experimental and clinical investigations are needed.

Selenium

Selenium, a trace element necessary for cellular function in many organisms, is a co-factor for the antioxidant enzyme glutathione peroxidase[95]. Glutathione peroxidase catalyses the reduction of both hydrogen peroxide and lipid hydroperoxides[96] and as such acts as an intracellular defence against free radical injury[97]. Nowadays, the role of micronutrients, in particular selenium, is receiving increased attention. Lower levels of selenium in toenails of AP patients and lower selenium concentrations in red blood cells of patients with severe AP have been found[40]. Selenium administration 24 h after induction of experimental AP has been demonstrated to be associated with amelioration of pancreatic injury and lung injury although it has not reversed the diminished serum selenium level[98]. Kuklinski *at al*[99] reported their clinical results of 4 years of selenium therapy. They concluded that an improvement in the prognosis of AP could be achieved if antioxidative selenium therapy with sodium selenite was introduced in time. In rare cases, total necroses and complications in organs only occurred in those patients who were admitted to this therapy too late. Wollschläger *et al*[100] reported that selenium therapy caused a significant increase in selenium, a moderate increase in glutathione peroxidase activity, and a significant decrease in MDA activity, while SOD remained unchanged in patients with AP. Lindner *et al*[101] did report, however, that substitution of sodium selenite had no beneficial effect of the clinical outcome of patients with AP (32 selenium administered, 35 placebo administered). On the other hand, Kocan *et al*[102] found selenium to be beneficial in decreasing inflammation in one patient with AP. The results of combination therapies including selenium will be discussed below.

RESULTS OF COMBINED ANTIOXIDANT THERAPIES

Recently we reported the beneficial effect of an antioxidant mixture of NAC and ascorbic acid on experimental AP in rats. The antioxidant mixture reduced tissue MDA levels and increased tissue CAT and glutathione peroxidase activities[1,42] in L-arginine-induced experimental AP. Hardman *et al*[103] have demonstrated that early exogenous anti-oxidant intravenous supplementation using a combination of NAC, selenium, and vitamin C reduces pancreatic injury in rats. However, a case-control study demonstrated no benefit from intravenous administration of these multicompound anti-oxidants in clinical

AP although critically, many patients in the clinical study received antioxidants relatively late in the course of the disease[104]. A randomized trial by Siriwardena *et al*[105] also failed to show any benefit to AP patients given selenium intravenously as part of a cocktail of antioxidants including NAC and vitamin C. On the other hand, Sateesh *et al*[106] demonstrated the beneficial effects of vitamin C and NAC on decreasing oxidative stress and improving antioxidant status in 23 patients with AP. They concluded that antioxidant supplementation associated with standard medical treatment may decrease the length of hospital stay and rates of complications in patients with AP, but a larger clinical trial is needed to support this hypothesis. The study of Bansal *et al*[107] showed that vitamin-based antioxidant therapy had no significant beneficial effect on organ dysfunction or on clinical outcomes in severe AP during the hospital stay. They administered vitamin A (intramuscularly), E (orally) and C (intravenously) together for a period of 14 d. Kuklinski *et al*[108] showed the beneficial effect of an adjuvant antioxidant therapy with selenium and D-alpha-tocopherol in 90 patients with necrotizing or mild AP. They reported that the average lethality rate of 34% fell to 1.1%. This study represents the vital benefits of antioxidant therapy. Uden *et al*[109] administered organic selenium, beta carotene, vitamin C, vitamin E and methionine to patients with recurrent pancreatitis (idiopathic chronic 8, alcoholic chronic 7, and idiopathic acute 5) and they reported the beneficial role of antioxidants in pain reduction. Recently, Zhao *et al*[110] reported the significant beneficial effects of the combination of ebselen and ethylhydroxyethyl cellulose (EHEC) on severe AP in Sprague Dawley rats. The mixture prevented pancreatitis- induced multiple organ injury. Ebselen (2-phenyl-1,2-benzisoselenazol-3(2H-one) is a non-toxic selenoorganic drug with anti-inflammatory, antiatherosclerotic, and cytoprotective properties that downregulates the production of OFRs[111,112]. Ebselen is a mimic of glutathione peroxidase that also reacts with peroxynitrite and can inhibit enzymes such as lipoxygenases, NO synthases, nicotinamide adenine dinucleotide phosphate oxidase, protein kinase C and H(+)/K(+)-ATPase[113,114]. The combination of ebselen and EHEC may be a new potential for treatment of severe AP[110].

While the trial clearly showed that the given combination of antioxidants was not effective in patients with AP when administered intravenously, antioxidants administered through another route may be beneficial, given that the benefits of enteral versus parenteral nutrition in patients with AP are well proven[115,116]. In particular, a growing body of clinical evidence from other disease settings suggests that supplementation of enteral nutrition with antioxidants can be beneficial[117,118].

In conclusion, based on the reported experimental studies, using antioxidant regimens in the management of AP as a supplement and combined with traditional therapy is rational and reasonable. If this hypothesis is correct, antioxidant therapy should reduce the inflammatory process involved in pancreatitis and thereby accelerate the recovery rate. Some of the antioxidants have been shown to be beneficial in the treatment of human AP. However, the present studies indicate that insufficient clinical data support using antioxidants alone or in combination with conventional therapy in the management of AP. Further double blind, randomized, placebo-controlled clinical trials with a larger sample size need to be conducted.

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