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Effectiveness and therapeutic value of phytochemicals in acute pancreatitis: A review

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ABSTRACT

Background: Acute pancreatitis (AP) is an inflammatory disorder of the pancreas that can lead to local and systemic complications. Repeated attacks of AP can lead to chronic pancreatitis, which markedly increases the probability of developing pancreatic cancer. Although many researchers have attempted to identify the pathogenesis involved in the initiation and aggravation of AP, the disease is still not fully understood, and effective treatment is limited to supportive therapy.
Methods: We aim to summarize available literature focused on phytochemicals (berberine, chlorogenic acid, curcumin, emblica officinalis, ellagic acid, cinnamtannin B-1, resveratrol, piperine and lycopene) and discuss their effectiveness and therapeutic value for improving AP.
Results: This study is based on pertinent papers that were retrieved by a selective search using relevant keywords in PubMed and ScienceDirect databases.
Conclusions: Many phytochemicals hold potential in improving AP symptoms and may be a valuable and effective addition to standard treatment of AP. It has already been proven that the crucial factor for reducing the severity of AP is stimulation of apoptosis along with/or inhibition of necrosis. Supplementation of phytochemicals, which target the balance between apoptosis and necrosis can be recommended in ongoing clinical studies.

Introduction

Acute pancreatitis (AP) usually occurs as a result of cholelithiasis or excessive alcohol consumption. This disease, in its acute form, can even lead to death. Among the causes of AP there are: cholelithiasis, alcohol abuse, hyperlipidemia, use of some medicines, serious abdominal injuries, bulimia, and mutations of genes that activate enzymes secreted by the pancreas. It may happen, however, that the causes of the disease cannot be recognized; in that case it is called idiopathic AP [1–4].

Calcium ions (Ca^{2+}) act as an electrolyte and are critical to the health of the muscular, circulatory, and digestive systems. Calcium signaling also plays a central role in the regulation of digestive enzymes and fluids secretion by the exocrine pancreas. Excess levels of Ca^{2+}, emerging from heightened release from endoplasmic reticulum Ca^{2+} stores inside the cell, elevated Ca^{2+} access through the cytoplasmic membrane and Ca^{2+} pump defects 5,6 are characterized as key factor in the pathogenesis of pancreatitis (Fig. 1.)

The essence of the disease is an inflammatory process that leads to the self-digestion of the organ by pancreatic enzymes due to acinar cell injury. When such a process begins, part of the pancreas can be completely destroyed. Pancreatic enzymes digest not only the organ itself, but also the walls of blood vessels and the pancreas wall adjacent to the gastrointestinal tract, which can lead to its perforation. Self-digestion of the organ contributes to a very strong local or generalized inflammation, and thus to a multi-organ failure, which resembles sepsis [5–7].

The revised classification of AP characterizes two phases of the disease: early and late. Severity is characterized as mild, moderate or severe, which are defined based on whether the predominant response to cell injury is inflammation (mild) or necrosis (severe). In mild acute pancreatitis, there is inflammation and edema of the pancreas. Moderately severe AP is defined by the emergence of transient organ failure, local complications or intensification of comorbidities. In severe acute pancreatitis, there is necrosis of the pancreas, and nearby organs may become injured [8,9]. As part of the initial injury there is an extensive inflammatory response due

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Abbrevations

AP	acute pancreatitis
AP-1	activator protein −1
BBR	berberine
CDE	choline-deficient ethionine-supplemented
CGA	chlorogenic acid
COX-2	cyclooxygenase-2
EA	ellagic acid
H_2O_2	hydrogen peroxide
IL	interleukin
ICAM	intercellular adhesion molecule
iNOS	inducible nitric oxide synthase
JNKs	c-Jun N-terminal kinases
LOX-5	lipoxygenase-5
MAPK	mitogen activated protein kinases
MIF	migration inhibitory factor
MMPs	metalloproteinases
MPO	myeloperoxidase
NF-κB	nuclear factor kappa B
PGC1- α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PSCs	pancreatic stellate cells
ROS	reactive oxygen species
TNF-α	tumor necrosis factor alpha
TRAF1	TNF receptor-associated factor 1
TxA2	thromboxane A2

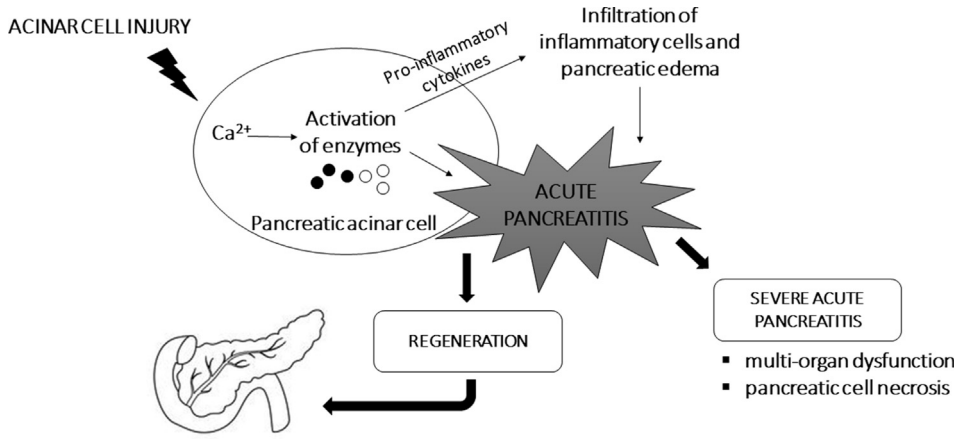

Fig. 1. Mechanisms of acinar cell injury in acute pancreatitis. The calcium ion is a key intracellular messenger that controls normal secretion by the pancreatic acinar cell. There are many causes that may lead to an overload of calcium ions, e.g. gallstones, alcohol abuse, hyperlipidemia, mutations of genes, trauma etc. The abnormal calcium signaling may lead to infiltration of inflammatory cells and pancreatic edema through activation of premature trypsinogen and vacuolization or even acinar cell death what consequently induces acute pancreatitis (based on Bai HX, Lowe ME, Husain SZ. What have we learned about acute pancreatitis in children? J Pediatr Gastroenterol Nutr. 2011; 52 (3):263 [103], modified).

to pancreatic cells synthesizing and secreting inflammatory mediators: primarily tumor necrosis factor (TNF-α) and interleukin 1 (IL-1). A hallmark of AP is a manifestation of the inflammatory response, namely the recruitment of neutrophils to the pancreas. The inflammatory response leads to the secondary manifestations of pancreatitis: hypovolemia due to increased capillary permeability, acute respiratory distress syndrome, disseminated intravascular coagulations, renal failure, cardiovascular failure, and gastrointestinal hemorrhage.

The therapy of mild form of AP consists of a 3–4-day fasting, intravenous fluid therapy and administration of painkillers. When nausea and abdominal pain subside, the patient may eat small portions of easily digestible foods. If the inflammation was caused by gallstones, removal of the stones from the common bile duct is necessary and the gallbladder should be removed. The challenge for physicians is to treat the severe form of pancreatitis, as no effective therapy has been developed yet. In the first hours or days of AP complications may occur and treatment is necessary to prevent the blood from thickening, preventing the spread of inflammation. Treatment of emerging complications such as kidney or lung injury is also extremely important. The patient must be intensively irrigated; painkillers are given and parenteral nutrition is often used. If there is a generalized infection, antibiotics are necessary. Pancreatic surgery is a last resort; depending on the severity of the inflammation, the operation may consist in the removal of the entire organ or part of it with the duodenum [1–5,7].

As therapeutics targeting the underlying pathology of AP are lacking, several new agents are under investigation. Recently, a great attention has been drawn to the repair and regeneration process in experimental models based on the treatment of AP using phytochemicals (Table 1). Some of them (curcumin and piperine [10] along with resveratrol [11]) have already been included in clinical trials in the treatment of AP what reveals their undeniable therapeutic value (Table 2). Here we will focus on berberine, chlorogenic acid, curcumin, emblica officinalis, ellagic acid, cinnamtannin B-1, resveratrol, piperine and lycopene [12–21].

Characterization of the phytochemicals in acute pancreatitis treatment

Berberine

Berberine (BBR) has a very positive effect on the intestinal function and regulation of the intestinal lining. Damage to the lining of the intestine occurs in the case of leaky intestinal syndrome and autoimmune diseases. This disorder is also associated with abnormalities in the blood-brain barrier. BBR limits the extent of inflammation by reducing the expression of TNF-α [22]. In

Table 1
Summary of the phytochemicals used in animal models of pancreatitis.

PHYTOCHEMICAL	DOSAGE AND ROUTE OF ADMINISRATION	MODEL	THERAPEUTIC EFFECT IN ACUTE PANCREATITIS	REF.
Berberine	1, 5, 10, 20 mg/kg BW; pretreatment – intraperitoneal injection	cerulein AP mouse model L-arginine AP mouse model	berberine (5 and 10 mg/kg) decreased the serum levels of amylase and lipase through the activation of the JNK pathway	12
Chlorogenic acid	20 and 40 mg/kg BW; pretreatment – intraperitoneal injection	L-arginine AP mouse model	chlorogenic acid decreased the histological severity of pancreatitis and pancreatitis-associated lung injury; it also decreased the levels of pancreatic enzyme activity and reduced the serum and pancreatic levels of MIF	30
Curcumin	100 mg/kg BW; pretreatment – intraperitoneal injection	severe AP rat model	curcumin decreased amylase serum level as well as cytokines (IL-10 and TNF-α) along with reduction and down-regulation of TLR4 and NF-κB expression	35
Amla	100 mg/kg BW; treatment – orally	L-arginine AP rat model	amla decreased serum levels of lipase, amylase and IL-10	16
Ellagic acid	85 mg/kg BW; treatment – orally	L-arginine AP rat model	ellagic acid reduced inflammatory and oxidative stress in pancreatitis and caused improvements in the fatal damage	73
Resveratrol	20 mg/kg BW; treatment – intravenous injection	severe AP rat model	resveratrol attenuated changes of both histopathologic and biochemical markers induced by severe AP	82
	10 mg/kg BW; pretreatment – intraperitoneal injection	cerulein AP rat model	resveratrol reduced histological damage as well as hyperamylasemia and hyperlipidemia; it also decreased serum levels of pro-inflammatory cytokine IL-1β and increased anti-inflammatory cytokine IL-10	85
Piperine	50 mg/kg BW; pretreatment – intraperitoneal injection	cerulein AP mouse model	piperine reduced the production of TNF-α, IL-1β, and IL-6 as well as cell death, amylase and lipase activity, and cytokine production in isolated cerulein-treated pancreatic acinar cells along with inhibition of MAPKs	20
Lycopene	50 mg/kg BW; pretreatment – intraperitoneal injection	cerulein AP rat model	lycopene protected the pancreatic tissues from oxidative damage through the inhibition of neutrophil infiltration and lipid peroxidation	21

BW = body weight.
AP = acute pancreatitis.

Table 2
Clinical trials with phytochemicals used as potential treatment in pancreatitis.

PHYTOCHEMICAL	STUDY DESIGN	CLINICAL TRIAL STATUS	CLINICAL TRIAL REGISTRATION NUMBER	REFERENCE
Curcumin and piperine	Randomized controlled trial	Pilot study	Not mentioned	10
Resveratrol	Multi-center, single-blinded, randomized controlled trial	Phase 4	NCT02947932	11

addition, BBR also buffers the level of pathogens in the gut and affects the production of short-chain fatty acids that strongly affect the activation of AMPK kinase, which in turn stimulates the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1- α), one of the epigenetic elements affecting a number of important metabolic processes in the body [23]. BBR has antibacterial, antiviral and antiparasitic effects and can be successfully used as a supplement contributing to the reduction of anaerobic bacteria in the gut [22–24].

BBR which is a well-known plant alkaloid, is reported to have anti-inflammatory activity in many diseases and probably can be used as a drug in the treatment of AP [12,25,26]. This has already been stated by Sun-Bok Choi et al. [12] who characterized the effect of BBR while using different mouse models of AP – cerulein (mild and early phase of AP) and L-arginine (severe necrotizing and early to late phase of AP) induced. The effects of BBR on the pancreatic and body weight ratio, serum amylase and lipase activities, levels of pro-inflammatory mediators such as TNF-α and interleukin (IL-1β, IL- 6) and levels of inducible nitric oxide synthase (iNOS) in an established mouse model of cerulein-induced AP were evidenced. Moreover, pancreatic and pulmonary histological changes along with decreased myeloperoxidase (MPO) activity have been noted. In addition, Sun-Bok Choi et al. examined the activation of mitogen activated protein kinases (MAPKs) and nuclear factor kappa B (NF-κB) to determine the inhibitory mechanisms of BBR in AP. It has been clearly stated that BBR inhibits cerulein induced AP through suppression of the activation of the c-Jun N-terminal kinases (JNKs) signaling pathways. Another study [25] stated that administration of BBR significantly inhibited histological damage to the pancreas and lung and decreased serum level of amylase and lipase, myeloperoxidase activity, cytokine production, and the mortality rate of the mice in pancreatitis and pancreatitis-associated lung injury in choline-deficient ethionine-supplemented (CDE) diet–induced severe AP. Furthermore, administration of BBR inhibited activation of NF-κB, JNKs, and p38 in the pancreas during CDE diet. The above mentioned results provide scientific evidence for the continuing development of medicines based on BBR as a potential drug for AP as well as a beneficial agent to regulate AP.

Chlorogenic acid

Chlorogenic acid (CGA) is an ester of quinic acid and caffeic acid, an organic chemical compound from the group of polyphenols. CGA occurs in plants, mainly in green (unroasted) coffee beans, cocoa leaves and seeds, yerba mate (dried, ground leaves and sticks of yerba mate), hawthorn, yam, artichoke, blueberry, chokeberry and mulberry, tomatoes, raw potatoes, but also in honey and some herbs. In smaller quantities it can also be found in peaches, apples, apricots, cherries, plums, black currants or blackberries [13,27,28].

CGA suppresses the generation of reactive oxygen species (ROS) and may be considered as a pharmaceutical agent to ameliorate atherosclerosis by preventing cell damage from ROS and therefore protecting endothelial cells against injury induced by lipopolysaccharide [29].

Ohkawara et al. [30] evaluated the protective effect of CGA on the inflammatory damage of pancreas and lung in mice with L-arginine-induced AP. In their study mice were intraperitoneally injected with CGA (20 and 40 mg/kg) 1 h before administration of L-arginine. This pretreatment decreased the histological severity of pancreatitis and pancreatitis-associated lung injury. Moreover,

administration of CGA decreased the levels of pancreatic enzyme activity. Interestingly, CGA reduced the serum and pancreatic levels of macrophage migration inhibitory factor (MIF) – a pro-inflammatory cytokine, which is implicated in cancer (e.g. it is found in many human cancer and cancer-prone inflammatory diseases, including chronic pancreatitis and pancreatic cancer) and may be characterized as critical mediator of severe acute pancreatitis [30–32]. This gives grounds for further CGA studies for the treatment of AP.

Curcumin

Curcumin is a natural polyphenolic compound derived from the long-nourishing rhizome, otherwise known as Indian turmeric, grown in India, China and in Southeast Asia (Indonesia, Thailand, Vietnam and Philippines). It is a plant originating from the ginger family, showing a wide range of biological activities. In traditional Chinese medicine, it was used to relieve indigestion and to treat hard to heal wounds and scars. It was also beneficial for various stomach and liver problems. Currently, widely conducted studies show its anti-inflammatory, antioxidant and anticancer effects as well as antibacterial, antiviral and antifungal properties. The beneficial effect of curcumin may be partly explained by its diversity – curcumin affects proteins, enzymes, cytokines, transcription factors and growth factors [33,34]. For example, curcumin can slow the secretion of glucose into the bloodstream after a meal and increase the sensitivity of cells to insulin. It is also a powerful antioxidant. The literature emphasizes its antibacterial, antiviral and antifungal properties [33–37].

The anti-inflammatory properties of curcumin are associated with impaired activation of NF-κB [35]. The proteins whose expression is regulated by this transcription factor include pro-inflammatory cytokines (IL-1, IL-2, IL-6, IL-8), interferons, adhesion molecules (ICAM-1, VCAM-1) and some enzymes (COX-2, cyclooxygenase-2 and LOX-5, lipoxygenase-5). It is therefore understandable that inhibition of NF-κB activity reduces the expression of genes responsible for the formation of proteins involved in the inflammatory process [14,35].

Zhong et al. [35] demonstrated the protective effect of curcumin in a rat model of severe AP via the involvement of TLR-4/NF-κB signaling pathway. Application of curcumin resulted in lower ascites volume and amylase serum. The levels of serum cytokines IL-10 and TNF-α were also significantly reduced after curcumin treatment, as evident from ELISA analysis. RT-PCR quantification showed down-regulation of TLR4 and NF-κB expressions as a function of curcumin treatment.

Other studies show that curcumin attenuates inflammation in a severe AP animal model by regulating TRAF1/ASK1 signaling [14]. It has been observed that pre-treatment with curcumin reduced the concentrations of IL-6 and TNF-α in serum and ascites, as well as the ascites volume and amylase activity in severe AP rats. Pre-treatment with curcumin reduced the expression of TNF receptor-associated factor 1 (TRAF1), IL6, and TNF-α in the pancreas. It has also been evidenced that curcumin significantly decreases serum amylase, Cr and blood urea nitrogen levels, and alleviates pancreatic and renal histological changes and downregulates renal protein levels of JAK2/STAT3 pathway components in severe AP in rats [38]. The molecular mechanism of curcumin-mediated amelioration of acute renal injury may be associated with the suppression of the abovementioned pathway to reduce expression of TNF-α and IL-6 levels. To conclude, the findings of the study revealed the potential use of curcumin for the prevention and treatment of severe AP and the associated renal injuries.

Currently there are several studies in the preclinical phase [36,39]. Of note, their results are positive and encourage randomized trials [10]. However, despite the fact that curcumin is safe even at high doses in humans, it also exhibits low bioavailability, probably due to poor absorption, fast metabolism, and rapid systemic elimination of this compound [40–43]. Hence, it seems important to create a formulation that is more bioavailable.

Amla

Amla (*Emblica officinalis)* is a fruit that due to its medicinal properties has been used in India for centuries. In Ayurveda, all parts of the plant, not only fruit, are used for rejuvenating purposes. Fresh fruits are high in ascorbic acid (vitamin C), reaching up to 445 mg per 100 g [44], stable and particularly well absorbed and metabolically active [45]. Amla also contains gallic acid, flavonoids and ellagic acid. Such complex exerts anti-exudative, anti-inflammatory, antioxidant and antiradical effects. Gallic, ellagic and ascorbic acids inhibit proliferation of cancer cells (antitumor activity), and stabilize the structure of cell membranes and epithelia. Together with flavonoids, they seal and strengthen the endothelia of blood vessels. They also have anti-microbial and fungistatic properties [46]. Powdered fruit and fruit extracts as well as powdered leaves are ingredients of preparations referring to traditional Ayurvedic medicine, with antiviral, antimycotic (antifungal), antibacterial and immunostimulating effect. Amla works well with gastrointestinal catarrh, gastritis, intestinal inflammation and haemorrhoids, as well as by supporting the treatment of colon cancer [47,48]. Leaf folate preparations regulate the level of sugar and cholesterol in the blood [49].

Sidhu et al. [16] stated that amla may be beneficial for treating AP in L-arginine rat animal model of AP. Serum levels of lipase and IL-10 were decreased in comparison to the arginine group and nucleic acid content, rate of DNA synthesis, pancreatic proteins, and pancreatic amylase content were significantly enhanced. Histopathological examination showed consequently lower total scores in the treatment group. Of note, Vitamin C was found to be less efficacious than *E. officinalis* for all outcome parameters.

Ellagic acid

Ellagic acid (EA) is an antioxidant found in many species of fruits and vegetables. The rich sources of EA are berries, mainly strawberries, raspberries, cranberries, grapes, as well as walnuts. Studies in animal models have shown that EA is metabolized by the intestinal microflora in the small intestine. EA and its metabolites after absorption are localized in the lung tissues and in smaller amounts in the liver [50].

The biological effect of EA on human skin cells is manifested primarily by inhibiting the activity of metalloproteinases (MMPs) – enzymes decomposing components of the cellular matrix and decreased expression of intercellular adhesion molecule (ICAM) which is involved in the development of the inflammatory process [51]. EA is able to prevent the development of cells infected with human papillomavirus (HPV), which is closely associated with cervical cancer [52].

On the basis of many studies, it was found that EA has potent anticancer properties. Research on breast, pancreatic, pharynx, skin, lung, colon and prostate cancers showed that EA, after reaching the tumor cell within 48 h, inhibits tumor cell divisions, and after 72 h it causes death of these cells [53–61]. This effect of EA could result from its ability to eliminate free radicals; and/or inhibition of pro-carcinogenic signaling pathways [62–66]. Namely, *in vitro* studies have shown that EA protects cells from oxidative damage induced by hydrogen peroxide [67]. Moreover, reports show that EA has the ability to induce detoxification of NADPH and quinone reductase enzymes, which display protective

activity against chemical agents [68]. The chemoprotective action of EA may be associated with a decrease in the rate of metabolism of carcinogens by P450 enzymes [69] and an increase in the expression and activity of the enzymes of the second phase of detoxification [70]. For example, EA significantly increased the *in vitro* activity of S-glutathione transferase, an enzyme responsible inter alia for the detoxification processes [71].

Masamune et al. [72] assessed the effects of EA on the activation and cell functions of pancreatic stellate cells (PSCs), which were isolated from rat pancreas tissue and used in their culture-activated, myofibroblast-like phenotype. EA suppressed the expression of IL-1β- and TNF-α-induced activation of activator protein 1 (AP-1) and MAPK, but not of NF-κB. In addition, EA inhibited transformation of freshly isolated cells to an activated, myofibroblast-like phenotype. Summarizing, EA constrained key cell functions and activation of PSCs. What is important, stellate cell proliferation and the expansion of their pool are a fundamental feature of pancreatic fibrosis.

Yılmaz et al. [73] determined that EA is an effective biochemical and histological therapeutic agent for the treatment of inflammation and oxidative stress in L-arginine induced AP in rats. The healing effects of EA on inflammatory and oxidative stress were confirmed by histopathological and biochemical evaluations of the pancreatic tissue. EA was beneficial in the treatment of AP through the reduction of serum levels of IL6, IL-1β, and TNF-α in the AP-EA group compared to the control − AP group.

Cinnamtannin B-1

Cinnamtannin B-1 is an A-type proanthocyanidin contained in several plant species such as *Laurus nobilis* L., *Vaccinium vitis-idaea*, *Parameria laevigata*, *Cinnamomum zeylanicum*, *Lindera umbellata*, and *Metaxya rostrata*. It is a potent antioxidant as well as protective agent against oxidative stress and apoptosis in human platelets. It has inhibitory activity against COX-2 *in vitro* [74,75].

Gonzalez et al. [74] examined the effect of cinnamtannin B-1 against various concentrations of H_2O_2 hydrogen peroxide (H_2O_2) in the mouse pancreatic acinar cells. It was concluded that the beneficial effects of cinnamtannin B-1 appear to be mediated by reducing the intracellular Ca^{2+} overload and intracellular accumulation of digestive enzymes evoked by ROS, which is a common pathological precursor that mediates pancreatitis. Moreover, these results support the usage of cinnamtannin B-1 as a potential treatment against oxidative stress-derived deleterious effects on cellular physiology.

Resveratrol

Resveratrol is a natural phenolic compound, occurring among others in grapes, peanuts and red wine. Resveratrol is often used in obesity disorders due to its ability to reduce the volume of adipose tissue [76–78]. It is also a component of supplements supporting the functioning of the endocrine system (increases testosterone levels and lowers the level of estrogen) and antioxidant complexes, and is used to detoxify the body [63,76]. Studies on animals and cell models have shown that resveratrol displays anti-cancer, anti-inflammatory and cardioprotective properties [59,79,80]. It also prolongs life in yeast (*Saccharomyces cerevisiae*), fruit fly (*Drosophila melanogaster*), nematode (*Caenorhabditis elegant*), fish (*Nothobranchius furzeri*) and mice [79]. Anti-inflammatory properties of resveratrol are associated with inhibition of expression of COX-1 and COX-2, as well as thromboxane A2 (TxA2) and prostaglandin synthesis [81]. Resveratrol has been shown to effectively induce apoptosis in the pancreas as well as inhibit serum amylase release and inflammatory reactions, suppress microcirculatory disturbances, and alleviate pancreatic pathological injuries through the up-regulation of Fas ligand expression and the down-regulation of the levels of angiotensin II, endothelin, nitric oxide and TNF-α [82–84].

The antioxidant and immunomodulatory properties of resveratrol may supply a promising chemopreventive approach in AP prevention. It has been stated that resveratrol pretreatment reduces histological damage induced by cerulein treatment, as well as hyperamylasemia and hyperlipidemia [85]. As numerous studies showed that resveratrol could effectively inhibit the progression of severe AP, the clinical trial has been designed [11]. The purpose of this study is to determine whether oral resveratrol pre-endoscopic retrograde cholangiopancreatography is effective on control of post-endoscopic retrograde cholangiopancreatography pancreatitis.

Piperine

Piperine is a piperidine derivative found in the top layer of black pepper fruits (*Piperis nigri*). It is a colorless or creamy-yellow, crystalline substance soluble in petrol, chloroform, ethanol, diethyl ether and pyridine [86]. Piperine intensifies the production of gastric juice and supports proper digestion; it stimulates the secretion of pancreatic and intestinal juices, increases appetite and shows diuretic and cleansing properties. Piperine facilitates the absorption of vitamins and minerals: vitamins from group B, beta-carotene, selenium, as well as coenzyme Q10 and resveratrol. It also possesses anti-inflammatory and antibacterial action, among others against *Staphylococcus aureus* and *Bacillus sphaericus* [18,87–90].

It has already been stated that piperine reduces the severity of cerulein-induced AP mouse model [20]. Administration of piperine orally (10, 50, or 100 mg/kg) 1 h before cerulein injection reduced histologic damage and MPO activity in the pancreas and ameliorated many of the examined laboratory parameters, including the pancreatic weight to body weight ratio, as well as serum levels of amylase and lipase and trypsin activity. Furthermore, piperine pretreatment reduced the production of TNF-α, IL-1β, and IL-6 during cerulein-induced AP. In accordance with *in vivo* results, piperine reduced cell death, amylase and lipase activity, and cytokine production in isolated cerulein-treated pancreatic acinar cells. In addition, piperine inhibited the activation of MAPKs.

Lycopene

Lycopene belongs to the family of carotenoids, natural dyes found in plants, mainly in tomatoes, red peppers and grapefruits [91]. Lycopene reacts easily with atomic oxygen and ROS [92] and its antioxidant activity is three times higher than other carotenoids [92,93]. Lycopene has also beneficial anticancer properties by obstructing the activity of carcinogens and inhibiting the cell division [91,93–95]. Lycopene may also play a crucial role in cholesterol metabolism: it prevents oxidation of LDL cholesterol and lowers overall cholesterol. In this way, lycopene reduces the risk of cardiovascular disease. Studies show that regular consumption of 60 mg of lycopene per day reduces the risk of myocardial infarction by lowering the level of cholesterol in 30–40% [18,91,96–98].

Özkan et al. [21] stated that lycopene administered intraperitoneally at a dose of 50 mg/kg per rat 15 min before the first cerulein injection protects the pancreatic tissues from oxidative damage, and this effect possibly involves the inhibition of neutrophil infiltration and lipid peroxidation. These results suggest that high dietary intake of tomatoes may have protective effects against AP.

Discussion and future perspectives

The main issue in AP, especially in the severe form of the disease, is the difficulty of planning clinical studies capable of giving reliable, statistically significant results regarding the benefits of various proposed therapeutic agents, previously tested in experimental settings. Moreover, the efficacy of the drugs already available, such as gabexate mesylate, lexipafant and somatostatin should be re-evaluated because of their short half-life and hence their limited clinical efficiency [99,100]. The current therapeutic guidelines for AP include the following: intravenous fluid replacement, dietary changes, analgesics, inhibitors of pancreatic secretion (somatostatin and its analogue, octreotide), L-arginine, calcium ion antagonists, and different inflammatory mediator inhibitors [101,102]. However, their use is rather disappointing. Hence, there is a renewed interest in phytomedicines, which lack severe adverse effects and may have benefits not only regarding the symptoms but also the disease evolution. Moreover, dietary agents such as phytochemicals generally remain non-toxic, even at relatively high-doses, and have immense potential due to their abundance and low cost. Studies in the recent years have shown that BBR, CGA, EA, amla, curcumin, cinnamtannin B-1, capsaicin, piperine, lycopene, resveratrol undoubtedly possess beneficial properties in preventing and ameliorating AP and/or triggering various biochemical mechanisms that lead to AP. However, only some were investigated in clinical studies (Table 2). Now further investigations are needed to understand the upper limit of consumption of these phytochemicals as well as to determine their effectiveness at various doses in humans. Finally, the search for new sources and new phytochemicals is warranted.

Authors' contributions

AT and JF provided the overall concept and framework of the manuscript; AT researched and identified appropriate articles, and wrote the manuscript; AT and JF revised the manuscript. Both authors read and approved the final manuscript.

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