Possible Synergistic Therapeutic Role of Taurine and Curcumin on Cerulein-Induced Acute Pancreatitis in Rats

Walaa A. M. El-Nahrawy[1] and Mohamed Islam A. H.[2]

[1]Zoology Department, Women's Collage for Arts, Education & Science, Ain Shams University
[2]Biological Applications Department, Nuclear Research Center, Atomic Energy Authority, Egypt.
*walaa_yao@yahoo.co.uk

Abstract: Acute pancreatitis is an inflammatory condition of the pancreas characterized clinically by abdominal pain and elevated levels of pancreatic enzymes in the blood. A number of conditions are known to induce this disorder with varying degrees of certainty. However, the pathogenesis of this disorder is not fully understood. The current study comprised two experiments; the first was carried out to compare the levels of pancreas tumor markers and pancreas function as a result of cerulein treatment which experimentally induced acute pancreatitis. In the second experiment, pancreatitis rats groups were treated with taruine or curcumin and their mixture. A significant elevation in pancreatic tumor markers profile (CEA, CA19.9, CA72.4 and CA242) was occurred as a result of cerulein treatment which experimentally induced acute pancreatitis. Also, a significant increment in the activities of α-amylase and lipase accompanied with a significant elevation in the concentration of TAP was pronounced in pancreatitis rats group. On the other hand, a significant reduce in the content of glutathione (GSH) and in the activity of glutathione peroxidase (GpX) occurred. The concentration of thiobarbituric acid reactive substances (TBARS) and MOP in pancreatic tissue was elevated as a result of cerulean treatment. In the second experiment, all pervious parameters were corrected as a result of taruine or curcumine administration dependent on time of treatment .The best ameliorating effect occurred in all previous parameters in rats group which treated with both antioxidants (taruine & curcumin) dependent on time of administration. These findings are consistent with the concept that taruine, curcumin or their mixture is an antipancreatitis agent. The underlying mechanisms of these effects were discussed according to variable researches.
[Walaa A. M. El-Nahrawy and Mohamed Islam A. H.Possible Synergistic Therapeutic Role of Taurine and Curcumin on Cerulein-Induced Acute Pancreatitis in Rats. Journal of American Science 2011;7(7):485-495].(ISSN: 1545-1003). http://www.americanscience.org.

Key word : Cerulein , Acute Pancreatitis, Curcumin , Taurine , pancreatic tumor marker.

1. Introduction:

Pancreatitis is the inflammation of the pancreas, an organ that produces several enzymes to aid in the digestion of food, as well as the hormone insulin, which controls the level of sugar (glucose) in the blood. The pancreas is located in the upper abdomen behind the stomach. When the pancreas is inflamed, the body is not able to absorb all the nutrients it needs (Schoenberg *et al*., 1994). Pancreatitis may be either acute (sudden and severe) or chronic. Both types of pancreatitis can cause bleeding and tissue death in or around the pancreas (Uomo *et al*., 1999 , Toouli *et al*., 2002 and Gultekin 2007) .

Severe acute pancreatitis is characterized by acinar cell injury with extensive tissue necrosis, inflammation, and hemorrhage. In most patients it is associated with remote organ failure, sepsis, and a high death rate. In the absence of a clear pathophysiologic concept of acute pancreatitis, current treatment strategies still focus on the management of subsequent complications rather than the cause of the disease. In the search of an improved therapeutic concept, increasing experimental and clinical evidence has arisen that oxidative stress and polymorphonuclear leukocytes play an instrumental role in the disease process (Dervenis *et al*., 1999; Uomo *et al*., 1999; Toouli *et al*., 2002 and Ceranowicz 2010).

In the twenty last years, a number of articles had been published on the treatment of acute pancreatitis in experimental model animals and most of them concerned rats (Byung *et al*., 2001; Alhan *et al*., 2006) and mice (Pastor & Frossard, 2001).

Taurine, 2-aminoethanesulphonic acid is an essential amino acid. It is present at high concentrations in many tissues. It plays important roles in numerous physiological functions including conjugation with bile acids, modulation of calcium levels and maintenance of osmolarity, antioxidation and stabilization of membranes (Huxtable, 1992 and Schrader, 2009). It was reported to have beneficial effects in various physiological and pathological conditions (Ahn *et al*., 2001; Chiba *et al*., 2002; Ozturk *et al*., 2003) by mainly diminishing production of reactive oxygen species (ROS). It also can prevent DNA damage at physiological concentrations (Messina & Dawson, 2000; Heibashy

& El-Nahrawy, 2008 and Heibashy & Sharoud, 2008). Taurine has also hepatoprotective effects such as inhibition of extracellular matrix accumulation in experimental liver fibrosis (Chen & Zhang, 1999 and Balkan *et al*., 2001) and improvement of liver function tests in fatty liver disease of children (Obinata *et al*., 1996). Hepatoprotective feature of taurine is attributed to its inhibitory activity on generation of ROS, which are known to play an important role in hepatic injury both in vitro and in vivo (Pietrangelo, 1996 and Svegliati -Baroni *et al*., 1998).

Moreover, several authors reported beneficial effects of taurine on histopathology and oxidative stress parameters in a rat model of CCl_4-induced liver fibrosis (Refik Mas *et al*., 2004 and Tasci *et al*., 2007) where remarkable histopathological improvement in taurine treated animals subjected to hepatotoxin was observed, and this was associated with oxidative stress reduction and hepatocellular apoptosis.

Curcuma longa Linn or turmeric is a tropical plant native to southern and southeastern tropical Asia. Curcumin is a diferuloylmethane present in extracts of the plant. Curcumin and it's derivatives that block or suppress the proliferation of tumor cells have potential as anticancer agents (Huang *et al*., 1994; Piper *et al*., 1998 and Lal *et al*., 2000). They have been shown to inhibit the proliferation of a wide variety of tumor cells, including B-cell and T-cell leukemia], colon carcinoma and epidermoid carcinoma cells. It has also been shown to suppress the proliferation of various breast carcinoma cell lines in culture.

Gukovsky *et al*. (2003) reported that curcumin ameliorates pancreatitis in two rat models. In both cerulein pancreatitis and pancreatitis induced by a combination of ethanol diet and low-dose curcumin, curcumin decreased the severity of the disease. They reported that the administration of curcumin markedly inhibited NF-kB and AP-1, IL-6, TNF-α, and iNOS in the pancreas. So, the authors suggested that curcumin may be useful for treatment of pancreatitis.

The objective of the current investigation is to clarify the possible correction correct in the estimated parameters which accompanied the induction of acute pancreatitis in rats after treatment with taurine or curcumin and their mixture. The underlying mechanisms through those antioxidants that counteracted acute pancreatitis in rats were discussed according to available published researches.

2. Materials and Methods

Ninety five adult male albino rats (Rattus rattus) were maintained in the animal-holding room under controlled environmental conditions (12/12 h light/dark cycle, 50% humidity, and 30°C) and fed rodent diet (NRC, 1977). They were housed in a well ventilated vivarum of Zoology Department, Women's Collage, Ain Shams University. The fresh tap water was available all the time. The animals were 8 - 10 weeks of age at the beginning of each study and caged in wire bottom galvanized metal wall boxes.

The study comprised two experiments; the first one was carried out to compare the levels of pancreas tumor markers and pancreas function as a result of cerulein treatment, to achieve this purpose, a comparison was done between a group of ten control rats received daily injections of normal saline (0.9%NaCl) for three days and other ten rats were daily injected subcutaneous with cerulein (Sigma Co. USA) at a dose of 40 µg/kg body weight for the same period as described by Niederau *et al*. (1990) to induce experimentally acute pancreatitis.

In the second experiment, five comparisons were made between normal control rats (n= 15 rats) and four groups of rats with experimentally acute pancreatitis. The first experimentally acute pancreatitis group was served as recovery group. The second acute pancreatitis group rats were treated (i.p.) with 500 mg taurine (Sigma Chem. Co., St. Louis, Mo., USA)/ kg b.wt/day for 30 days according to Byung *et al*. (2001). The third acute pancreatitis group rats were treated orally with 30 mg curcumin (Commercial curcumin was used)/ kg b.wt/day for 30 days according to Heibashy & Sharoud (2008). The fourth pancreatitis group rat was received both taurine and curcumin for the same previous period. All animal groups were divided into three intervals (10, 20 and 30 days and five rats in each interval).

At the end of each experimental period, blood samples were collected from each group by decapitation killing. Serum carcino-embryonic antigen (CEA) and the cancer antigens ($CA_{19.9}$), ($CA_{72.4}$) and (CA_{242}) were assayed by radioimmunoassay (RIA) kits using solid phase component system. (ICN Pharmaceuticals Inc, USA).

Serum α-amylase and lipase activities were estimated according to Garber & Wulff (1989) and Lott (1986) respectively using commercial ELISA kits (Diagnostic Automation, INC. USA). Serum trypsinogen activation peptide level was assayed by ELISA as described previously by Lee (2000).

After sacrifice, pancreases were obtained at the end of each experimental period and wash with saline solution (0.9 % NaCl). After washing, the kidneys were homogenized in ice-cold 0.25 M sucrose containing 1mM diethylenetriamine penta-acetic acid (1:1 w/v). Each sample was then centrifuged for 20 min at 20,000 g and 4°C. The supernatant was aspirated for measuring the content of reduced GSH

(Baker *et al*., 1990), thiobarbituric acid reactive substances (TBARS) concentration (Devasagayam & Tarachand,1987) and the activity of glutathione peroxidase (GPX) (Ursini *et al*., 1985) by the aid of ELISA technique and using commercial kits (IBL Gesellschaft, Hamburg, Germany).

The sequestration of neutrophils within the pancreas was evaluated quantity by tissue myeloperoxidase (MPO) activity using ELISA technique as described by Olsen & Little 1983. The kit was purchased from Gen Way Co. (USA).

Data were statistically analyzed using Student "t" test in the first experimental (Milton *et al*., 1986). Moreover, two way analysis of variance (ANOVA) followed by Duncan's multiple range test in the second experimental according to Snedecor & Cochran (1982).

3. Results and Discussion

In man, acute pancreatitis is a severe disease with a significant morbidity and mortality (Lerch & Adler, 1994). In order to better understand the underlying cellu'lar mechanisms of acute pancreatitis in humans, several experimental animal models of acute pancreatitis have been developed. So, acute pancreatitis is an inflammatory condition of the pancreas characterized clinically by abdominal pain and elevated levels of pancreatic enzymes in the blood. A number of conditions are known to induce this disorder with varying degrees of certainty. However, the pathogenesis of this disorder is not fully understood (Pezzilli *et al*., 2006).

The establishment of acute pancreatitis animal models makes enables the researchers to study the details of acute pancreatitis pathophysiology. It should be emphasized that the use of numerous acute pancreatitis animal models is essential because it ensures that the acute pancreatitis -related biological factors are not model-specific (or animal-specific). Traditionally, the discovery of key biological factors relied on classical strategies such as investigation of gene or protein expression during the episode of acute pancreatitis. In the recent decade, the development of transgenic animals should shed light on acute pancreatitis pathogenesis. Transgenic animals are the animals that carry a transgene in addition to their complement DNA. The target transgene is cloned by recombinant DNA technology, is delivered to recipient zygote or embryonic stem cells, and integrates into the host's own genome. The incorporation would result in either gain-of-function or loss-of-function, thus generating knock-in or knockout animal, respectively (Galli-Taliadoros *et al*., 1995 and Schafer *et al*., 2005).

In the current investigation, acute pancreatitis was induced in rats by the administration of 40 µg cerulein /kg b.wt/ for three days as described by Niederau *et al*. (1990). A significant elevation occurred in the tumor marker profile (CEA, $CA_{19.9}$, $CA_{72.4}$ and CA_{242}) as a result of cerulein administration in rats (Table 1). These results may be attributed to the elevation of free radical production, increasing lipid peroxidation concentration or defect in the immune system defense. Several studies have suggested that the elevation in the activities of phospholipase A2 (PLA2) and cyclooxygenase-2 (COX-2) may lead to pronounce acute pancreatitis in human (Hietaranta *et al*., 1999; Makela *et al*., 1999; Nevalainen *et al*., 2000; Ethridge *et al*., 2002; Zhou *et al*., 2004; Kihara *et al*., 2005) and in experimental animals (Yoshikawa *et al*., 1999; Tomita *et al*., 2004; Yan *et al*., 2004 and Camargo *et al*., 2005).

Table (1): Changes in serum tumor marker profile (CEA, CA19.9, CA72.4 and CA242) in acute pancreatic rats compared to those normal control ones.

Parameters	Normal rats (n=10)	Pancreatic cancer rats(n=10)
CEA (ng/ml)	0.23±0.006	3.18±0.042*
$CA_{19.9}$ (U/ml)	7.82±0.107	50.73±1.283*
$CA_{72.4}$ (U/ml)	4.19±0.091	21.41±0.216*
CA_{242} (U/L)	3.54±0.068	16.57±0.139*

- Values are expressed as mean ± SE. – n = number of rats.- * Means a significant (P< 0.001).

Phospholipase A2 (PLA2) is one of the enzymes that catalyzes the hydrolysis of phospholipids, the products of which are free fatty acids and lysophospholipids. Several types of PLA2 have been identified including group I, II, V,and X. Among these, group II PLA2 has been identified as a particularly important mediator during acute inflammation. Group II PLA2 can be activated by proinflammatory cytokines such as interleukin (IL) 1, IL-6, and tumor necrosis factor-α (Nevalainen *et al*., 2000 and Heibashy & Sharoud, 2008).

Elevated serum PLA2 activity, primarily of the group II isoform, has been detected in patients with infections and inflammatory diseases. Intraductal infusion of PLA2 alone or in combination with another substance like deoxycholate can induce acute pancreatitis in rats (Hietaranta *et al*., 1999 and Makela *et al*., 1999). Plasma group II PLA2 activity has been shown to be elevated in the taurocholate-

induced (Uhl *et al*., 1999) and deoxycholate-induced acute pancreatitis model (Furue *et al*., 1999). These observations are in good agreement with the findings in the clinical setting. Patients diagnosed with acute necrotizing pancreatitis have elevated serum PLA2 activity (Makela *et al*., 1999).

Cyclooxygenase (COX) is a key enzyme in the prostanoid system; it catalyzes the conversion of arachidonic acid to prostaglandin. Two isoforms of COX have been identified: the constitutively expressed COX-1 and the inducible COX-2. The expression of inducible COX-2 is controlled by certain inflammatory factors including IL-1 and tumor necrosis factor-α (Yan *et al*., 2004 and Heibashy & Sharoud, 2008). This rate-determining enzyme in prostaglandin synthesis may play an important role in the pathophysiology of acute pancreatitis. COX-2 expression was found to be upregulated in caerulein-induced pancreatitis in mice (Song *et al*., 2002) and rats (Yan *et al*., 2004 and Zhou *et al*., 2004).

In the current study, serum α-amylase, lipase activities and trypsinogen activation peptide (TAP) concentration were decreased significantly in cancer rats group (Table 2). These results may be due to disturbance inflammatory cytokines (IL-1 & IL-6), reactive oxygen species (ROS) and mediators of inflammatory pathways such as cyclooxygenase-2 (COX-2) and Nuclear Factor Kappa B (NFkB). However, they are associated with oncogene expression, silencing of tumor suppressor genes and affect the cell cycle, all of which may facilitate pancreatic carcinogensis. Moreover, mediators of the inflammatory response may also induce genetic damage, cell proliferation and inhibition of apoptosis in the pancreas. Because ROS contribute to the inflammatory process, evaluating the potential cancer protective effects of dietary antioxidants is a logical step in this area of research. These results were confirmed by Song *et al*. (2002); Yan *et al*. (2004); Zhou *et al*. (2004); Alhan *et al*. (2006); Tasci *et al*. (2007) and Buyukberber *et al*. (2009).

Table (2): Changes in serum α-amylase, lipase activities and trypsinogen activation peptide (TAP) concentration in acute pancreatic rats compared to those normal control ones.

Parameters	Normal rats (n=10)	Pancreatic cancer rats(n=10)
α-amylase (U/L)	186.47±2.593	935.274±6.386*
Lipase (U/L)	92.61±1.107	395.44±2.482*
TAP (ng/ml)	9.42±0.261	23.19±0.497*

- Values are expressed as mean ± SE. – n = number of rats.

The present study developed and characterized a new and highly reproducible rat model of acute pancreatitis using a dose of 40 µg cerulein/kg body weight. The administration of cerulein resulted in a significant decrease in the content of GSH and the activity of G_{px} while, the concentration of thiobarbituric acid reactive substances (TBARS) and the activity of myeloperoxidase (MPO) in tissues were significantly elevated in pancreatitis rats group (Table 3). These data may be attributed to the disturbance in the serum α-amylase, lipase activities and trypsinogen activation peptide (TAP) concentration, alteration in the cellular endoplasmic reticulum of pancreas or/ and histological changes (including accumulation of fluid, disruption of histo-architecture, acinar cell vacuolization, extensive acinar cell necrosis and neutrophilic infiltration) resembling acute pancreatitis in humans.

Table (3): Changes in GSH content, Gpx activity, TBARS, MPO concentrations in acute pancreatic rats tissue compared to their corresponding normal control ones.

Parameters	Normal rats (n=10)	Pancreatic cancer rats(n=10)
GSH (mg / g protein)	14.56 ± 0.493	6.93±0.275*
Gpx (µmol /min / g protein)	73.14 ± 1.062	42.36±0.684*
TBARS (nmol / 100mg Protein)	2.09 ± 0.069	4.27±0.089*
MPO (U/mg protein)	9.12±0.374	27.81±0.873

- Values are expressed as mean ± SE. – n = number of rats.- * Means a significant (P< 0.001).

Judging from these data, Malo *et al*. (2010) reported that acute pancreatitis is accompanied with disturbance in glutathione pool, inflammatory cytokines (IL-10 & TNF-α) and the formation of nitric oxide (NO) due to the disturbance in citrulline/NO cycle.

Taurine is a semi-essential sulphur amino acid derived from methionine and cysteine metabolism and promotes neurological function - neurotransmitter/neuromodulator, neurotrophin, antioxidant, and osmolyte (Gibson *et al*., 2007 and Heibashy & Sharoud, 2008).

The administration of taurine to acute pancreatitis rats led to a significant correction in all studied parameters dependent on time of treatment (Tables 4, 5 & 6). These results may be attributed to the magic physical and chemical characteristic powerful of taurine which immediately stop cancer from spreading and start killing existing cancer cells, acts as a free radical scavenger, decreases lipid peroxidation production via increases β-oxidation in the mitochondria matrix, rebuild the immune system and damaged tissue. So, the body can naturally transform or expel any tumorous masses and eliminate the causal factors that destroyed immune system in the first place. These results are in harmony with those obtained by Lee *et al*. (1992); Ebrahim *et al*. (2001) and Tasci *et al*. (2007&2008).

Lee *et al*. (1992) postulated that the protective action of taurine on oxidant-induced damages of tissue components including degradation of hyaluronic acid may be attributed to both its scavenging action on hypochloriate (HOCl) and chloramine and the complex formation of taurine with HOCl or NH_2Cl without scavenging action on oxygen free radicals.

The protective capacity of taurine was attributed to free radicals scavenging. Subjects treated with placebo showed a significant increase in the number of severely damage mitochondria after reprefusion, whereas the number of damaged and necrotic myocytes also increased significantly in these subjects after infusion. No such damage to mitochondria or myocytes was observed in the taurine treated subjects (Lee *et al*., 1992). The use of supplemental taurine as a physiological protective against lipid peroxidation was advocated by Gordon *et al*. (1986) who demonstrated the protection of hamaster bronchioles from acute NO_2-induced alterations. The authors outlined the mechanism through which acute ROS tissue damage is believed to act. NO2 and its highly ROS interact directly with plasma membrane of cell products, possibly via lipid peroxidation triggering a series of events that include the release of chemotactic factors and acute phase reactions responsible for the influx of neutrophils. Activation of neutrophils results in production of superoxide, free radicals and hydrogen peroxide (H_2O_2), which cause further epithelial damage. Activated neutrophils also release proteolytic enzymes that have the capacity to alter alveolar interstitial components. It was proposed by Gordon *et al*. (1986) and Cardin *et al*. (1999) that the protective activity of taurine may reside in its ability to become chlorinated in the presence of HOCL, thereby preventing the direct attack of this oxidant on cell membranes (Rock *et al*., 1996).

Turmeric, derived from the plant Curcuma longa, is a gold-colored spice commonly used on the Indian subcontinent, not only for health care but also for preservation of food and as a yellow dye for textiles. Curcumin has been shown to exhibit anti-oxidant, anti-inflammatory, antiviral, antibacterial, antifungal, and anticancer activities and thus has a potential against various malignant diseases, diabetes, allergies, arthritis, Alzheimer disease, and other chronic illnesses (Huang *et al*., 1994; Piper *et al*., 1998 and Lal *et al*., 2000)

These effects are mediated through the regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes. Curcumin exhibits activities similar to recently discovered TNF blockers (e.g; humira, remicade and enbrel), vascular endothelial cell growth factor blocker (e.g; avastin), human epidermal growth factor receptor blockers (e.g; erbitux, erlotinib, and geftinib), and HER2 blocker (Chattopadhyay *et al*., 2004; Hong *et al*., 2004 and Prasad *et al*., 2004 and Heibashy & El-Nahrawy; 2008).

Gukovsky *et al*. (2003) reported that curcumin ameliorates pancreatitis in two rat models. In both cerulein pancreatitis and pancreatitis induced by a combination of ethanol diet and low-dose curcumin, curcumin decreased the severity of the disease. Curcumin markedly inhibited NF-kB and AP-1, IL-6, TNFα, and iNOS in the pancreas. Based on these studies, Gukovsky *et al*. suggested that curcumin may be useful for treatment of pancreatitis.

Soni *et al*. (1992) examined the effect of curcumin on serum levels of cholesterol and lipid peroxides in 10 healthy human volunteers. A dose of 500 mg of curcumin per day for 7 days significantly decreased the level of serum lipid peroxides (33%), increased HDL cholesterol (29%) and decreased total serum cholesterol (11.63%). The results suggest curcumin as a chemopreventive substance against arterial diseases.

Numerous studies have been performed on the biotransformation of curcumin. Lin *et al*. (2000) showed that curcumin was first biotransformed to dihydrocurcumin and tetrahydrocurcumin and that these compounds subsequently were converted to monoglucuronide conjugates. Thus, curcumin-glucuronide, dihydro-curcumin-glucuronide, tetrahydrocurcumin-glucuronide and tetrahydrocurcumin are major metabolites of curcumin in mice.

To test the hypothesis that curcumin metabolites resemble their progenitor in that they can inhibit COX-2 expression, curcumin and four of its metabolites at a concentration of 20 mM were compared in terms of their ability to inhibit phorbol

ester-induced prostaglandin E2 (PGE2) production in human colonic epithelial cells. Curcumin reduced PGE2 levels to preinduction levels, whereas tetrahydrocurcumin, hexahydrocurcumin, and curcumin sulfate had only weak PGE2 inhibitory activity, and hexahydrocurcuminol was inactive. The results suggested that (a) the major products of curcumin biotransformation by hepatocytes occurred only at low abundance in rat plasma after curcumin administration and (b) metabolism of curcumin by reduction or conjugation generates species with reduced ability to inhibit COX-2 expression (Lin *et al*., 2000; Ishida *et al*., 2002; Gukovsky *et al*., 2003 and Heibashy and El-Nahrawy,2008). Because the gastrointestinal tract seems to be exposed more prominently to unmetabolized curcumin than any other tissue, the results support the clinical evaluation of curcumin as a colorectal cancer chemopreventive agent.

Treated acute pancreatitis rats with curcumin led to a significant amelioration in all studied parameters dependent on time of treatment (Tables 4, 5 & 6). These results may be due to the powerl of curcumin which suppresses the activation of the transcription factor NF-KB, which regulates the expression of proinflammatory gene products, downregulates the expression of COX-2, an enzyme linked with most types of inflammations; inhibits the expression of another proinflammatoryenzyme 5-LOX; downregulates the expression of various cell surface adhesion molecules that have been linked with inflammation; downregulates the expression of various inflammatory cytokines including TNF, IL-1, IL-6, IL-8 and chemokines and a potent antioxidant of curcumin which reduces free radical production and stabilizes cell membrane. These data are in agreement with those obtained by Chattopadhyay *et al*. (2004); Hong *et al*. (2004); Prasad *et al*. (2004); Lantz *et al*. (2005); Lee *et al*. (2005); Gulcubuk *et al*. (2006); Tunstall *et al*. (2006) and Heibashy & El-Nahrawy (2008).

While, prooxidants are consider mediators of numerous diseases, antioxidants are generally believed to delay or halt the disease. However, this paradigm is not always valid as most cytokines mediate their effects through prooxidant mechanisms. Reactive oxygen species (ROS) also play an important role in cell-mediated cytotoxicity (CMC) of the immune system. Numerous reports indicate that curcumin could mediate both prooxidant and antioxidant roles. First, curcumin could induce the expression of ROS, which plays an important role in the antiproliferative effects of this molecule (Prasad *et al*., 2004; Lantz *et al*., 2005 and Lee *et al*., 2005). Second, curcumin binds thioredoxin reductase (TR) and converts this enzyme to NADPH oxidase, thus leading to the production of ROS. Because TR is overexpressed in tumor cells, curcumin kills tumor cells through this mechanism. (Rao *et al*., 1995; Lal *et al*., 2000; Gulcubuk *et al*., 2006; Tunstall *et al*.; 2006 and Heibashy & El-Nahrawy, 2008). Third, curcumin suppresses lipid peroxidation (Gulcubuk *et al*., 2006; Tunstall *et al*.; 2006 and Heibashy & El-Nahrawy, 2008). Fourth, curcumin increases the expression of intracellular glutathione (Chattopadhyay *et al*., 2004; Hong *et al*., 2004 and Prasad et al., 2004 and Heibashy & El-Nahrawy; 2008). Fifth, curcumin could also play an antioxidant role through its ability to bind iron (Jiao et al., 2006).

All these reports combined suggest the ability of curcumin to modulate the redox status of the cells. So, curcumin can modulate the cellular action of various growth factors and cytokines. However, curcumin has the ability to downregulate the effect of epidermal growth factor (EGF) through downregulation of expression and activity of EGF receptors (Smith et al., 2004; Chen et al., 2006 and Kim et al., 2006). Curcumin downregulates the activity of human EGFR-2 (called HER2/neu) which is a growth factor receptor closely linked with cancer of breast, lung, kidney and prostate (Hong et al., 1999). Also, curcumin suppresses the action of intereleukin (IL-6) through the downregulation of STAT3 activation and modulates the action of TNF (Chattopadhyay et al., 2004; Hong et al., 2004 and Prasad et al., 2004 and Heibashy & El-Nahrawy; 2008).

Maximum amelioration occurred in tested parameters of acute pancreatitis rats treated with both antioxidants (Taurine and curcumin). These results may be attributed to the synergistic effects of both antioxidants which act as anti-cancer agents (Table 3).

In conclusion, this study substantiates that taurine and curcumin, through their marked antioxidant activities, coupled with favorable anti-cancer effects salvages in acute pancreatitis of rats induced by cerulein administration depending on the time of treatment.

Corresponding author
Walaa A. M. El-Nahrawy
Zoology Department, Women's Collage for Arts, Education & Science, Ain Shams University
walaa_yao@yahoo.co.uk

Table (4): Amelioration effects of the administration of tarurine or curcumin and their mixture on serum tumor marker profile (CEA, CA19.9, CA72.4 and CA242) in acute pancreatic rats

Parameters		Normal rats (n=15)	Pancreatic cancer rats(n=15)	Pancreatic cancer + Tarurine rats(n=15)	Pancreatic cancer + Curcumin rats(n=15	Pancreatic cancer + Tarurine + Curcumin rats(n=15)
CEA	10 Days	0.22 ± 0.005^{A}	3.26 ± 0.047^{B}	2.68 ± 0.039^{E}	2.86 ± 0.042^{H}	2.37 ± 0.038^{F}
	20 Days	0.23 ± 0.006^{A}	3.79 ± 0.052^{C}	2.41 ± 0.036^{F}	2.71 ± 0.039^{E}	2.03 ± 0.031^{G}
	30 Days	0.23 ± 0.005^{A}	3.86 ± 0.059^{D}	2.07 ± 0.032^{G}	2.47 ± 0.037^{F}	1.74 ± 0.028^{I}
$CA_{19.9}$	10 Days	7.86 ± 0.109^{A}	54.66 ± 1.292^{B}	46.52 ± 1.127^{E}	50.93 ± 1.238^{H}	40.88 ± 1.102^{F}
	20 Days	7.79 ± 0.104^{A}	58.37 ± 1.322^{C}	40.46 ± 1.039^{F}	45.82 ± 1.163^{E}	34.02 ± 1.083^{G}
	30 Days	7.83 ± 0.106^{A}	61.58 ± 1.419^{D}	33.81 ± 1.076^{G}	40.97 ± 1.114^{F}	28.56 ± 1.039^{I}
$CA_{72.4}$	10Days	4.21 ± 0.087^{A}	22.53 ± 0.227^{B}	18.02 ± 0.217^{C}	20.36 ± 0.221^{F}	16.23 ± 0.212^{D}
	20 Days	4.19 ± 0.092^{A}	22.71 ± 0.232^{B}	16.35 ± 0.211^{D}	17.98 ± 0.216^{C}	13.24 ± 0.197^{E}
	30 Days	4.22 ± 0.089^{A}	22.74 ± 0.238^{B}	13.04 ± 0.219^{E}	16.11 ± 0.214^{O}	10.18 ± 0.186^{G}
CA_{242}	10 Days	3.57 ± 0.071^{A}	20.35 ± 0.147^{B}	15.48 ± 0.126^{E}	16.87 ± 0.34^{H}	14.62 ± 0.125^{I}
	20Days	3.54 ± 0.069^{A}	25.02 ± 0.159^{C}	13.27 ± 0.118^{F}	14.58 ± 0.123^{I}	10.54 ± 0.105^{G}
	30 Days	3.55 ± 0.071^{A}	28.97 ± 0.168^{D}	10.59 ± 0.109^{G}	13.11 ± 0.123^{F}	7.48 ± 0.093^{K}

- Values are expressed as mean ± SE. – n = number of rats

$^{A,B,C,D,E,F,G,H.I,J,K,}$ Means with a common superscript within a row are not significantly different (P>0.05).

Table (5): Amelioration effects of the administration of tarurine or curcumin and their mixture on serum α-amylase, lipase activities and trypsinogen activation peptide (TAP) concentration in acute pancreatic rats

Parameters		Normal rats (n=15)	Pancreatic cancer rats(n=15)	Pancreatic cancer + Tarurine rats(n=15)	Pancreatic cancer + Curcumin rats(n=15	Pancreatic cancer + Tarurine + Curcumin rats(n=15)
α-Amylase (U/L)	10 Days	188.19 ± 2.612^{A}	1237.21 ± 8.357^{B}	911.32 ± 6.534^{D}	927.11 ± 6.613^{D}	811.42 ± 4.983^{G}
	20 days	185.47 ± 2.588^{A}	1391.41 ± 9.185^{C}	727.43 ± 5.937^{E}	731.69 ± 5.886^{F}	529.71 ± 4.589^{F}
	30 days	187.39 ± 2.595^{A}	1251.92 ± 0.059^{D}	538.11 ± 4.612^{F}	543.31 ± 4.722^{F}	310.27 ± 3.816^{H}
Lipase (U/L)	10 Days	93.12 ± 1.112^{A}	424.13 ± 2.932^{B}	336.21 ± 2.457^{D}	387.91 ± 2.712^{C}	281.14 ± 2.237^{E}
	20 days	92.78 ± 1.104^{A}	396.46 ± 2.717^{C}	272.93 ± 2.128^{E}	350.72 ± 2.426^{D}	201.91 ± 1.924^{F}
	30 days	92.94 ± 1.117^{A}	390.58 ± 2.687^{C}	198.36 ± 1.827^{F}	323.61 ± 2.398^{DF}	163.57 ± 1.492^{G}
TAP (ng/ml)	10Days	9.47 ± 0.263^{A}	25.31 ± 0.527^{B}	21.19 ± 0.482^{E}	23.64 ± 0.508^{H}	19.04 ± 0.388^{F}
	20 days	9.43 ± 0.261^{A}	27.56 ± 0.613^{C}	18.86 ± 0.429^{F}	21.24 ± 0.486^{E}	15.93 ± 0.364^{I}
	30 days	9.49 ± 0.258^{A}	30.71 ± 0.672^{D}	16.27 ± 0.387^{G}	15.13 ± 0.417^{I}	13.47 ± 0.319^{K}

- Values are expressed as mean ± SE. – n = number of rats

$^{A,B,C,D,E,F,G,H.I,J,K,}$ Means with a common superscript within a row are not significantly different (P>0.05).

Table (6): Amelioration effects of the administration of Tarurine or Curcumin and their mixture in GSH content, Gpx activity, TBARS, MPO concentrations in cute pancreatic rats tissue in acute pancreatic rats

Parameters		Normal rats (n=15)	Pancreatic cancer rats(n=15)	Pancreatic cancer + Tarurine rats(n=15)	Pancreatic cancer + Curcumin rats(n=15	Pancreatic cancer + Curcumin rats(n=15)
GSH (mg / g protein)	10 Days	14.52 ± 0.487^{A}	6.62 ± 0.265^{B}	7.58 ± 0.289^{D}	7.49 ± 0.291^{D}	8.22 ± 0.327^{E}
	20 days	14.61 ± 0.491^{A}	6.13 ± 0.239^{C}	8.32 ± 0.321^{E}	8.18 ± 0.316^{E}	9.81 ± 0.392^{F}
	30 days	14.57 ± 0.491^{A}	6.07 ± 0.228^{C}	9.76 ± 0.386^{F}	9.63 ± 0.379^{F}	11.57 ± 0.413^{G}
G_{PX} (µmol/min / g protein)	10 Days	73.31 ± 1.072^{A}	40.78 ± 0.663^{B}	47.24 ± 0.692^{D}	46.93 ± 0.687^{D}	49.87 ± 0.729^{E}
	20 days	71.97 ± 1.069^{A}	36.19 ± 0.614^{C}	50.43 ± 0.727^{E}	50.09 ± 55.78^{E}	56.31 ± 0.811^{F}
	30 days	72.58 ± 1.074^{A}	35.88 ± 0.597^{C}	56.12 ± 0.809^{F}	55.78 ± 0.789^{F}	60.57 ± 0.868^{G}
TBARS (nmol/ 100mg Protein)	10Days	2.11 ± 0.071^{A}	4.63 ± 0.092^{B}	4.09 ± 0.087^{D}	4.13 ± 0.089^{D}	3.72 ± 0.081^{E}
	20days	2.08 ± 0.069^{A}	4.91 ± 0.104^{C}	3.66 ± 0.078^{E}	3.74 ± 0.081^{E}	3.19 ± 0.075^{F}
	30 days	2.09 ± 0.068^{A}	5.05 ± 0.109^{C}	3.07 ± 0.072^{F}	3.13 ± 0.076^{F}	2.77 ± 0.073^{G}
MPO (U/mg protein)	10 Days	9.17 ± 0.371^{A}	29.34 ± 0.934^{B}	25.51 ± 0.782^{E}	27.82 ± 0.819^{H}	24.62 ± 0.718^{E}
	20 days	9.11 ± 0.369^{A}	33.78 ± 1.123^{C}	21.16 ± 0.734^{F}	24.36 ± 0.752^{E}	17.39 ± 0.641^{G}
	30 days	9.21 ± 0.378^{A}	36.85 ± 1.3598^{D}	16.84 ± 0.629^{G}	20.93 ± 0.714^{F}	12.04 ± 0.527^{K}

- Values are expressed as mean ± SE. – n = number of rats

$^{A,B,C,D,E,F,G,H.I,J,K,}$ Means with a common superscript within a row are not significantly different (P>0.05).

References:

Aggarwal, B.B.;Kumar, A. and Bharti, A.C. ,2003. Anticancer potential of curcumin: preclinical and clinical studies, Anticancer Res., 23 : 363–398.

Ahn,B.O.;Kim, K.H.; Lee, G.;Lee, H.S.; Kim, C.D.; Kim, Y.S.; Son, M.W.; Kim, W.B.;Oh, T.Y.and Hyun, J.H. ,2001. Effects of taurine on cerulein-induced acute pancreatitis in the rat. Pharmacology; 63: 1-7.

Alhan, E.; Türkyilmaz, S.; Erçin, C. Kaklikkaya, N. and Kural , B.V.,2006. Effects of omega-3 fatty acids on acute necrotizing pancreatitis in rats. Eur Surg Res.; 38:314-21.

Ammon, H.P. and Wahl, M.A. ,1991. Pharmacology of Curcuma longa, Planta Med., 57: 1–7.

Argent BE, Case RM. Pancreatic ducts ,1994. cellular mechanism and control of bicarbonate secretion. In: Johnson LR, Alpers DH, Christensen J, Jacobson ED, Walsh JH, editors. Physiology of the gastrointestinal tract. 3rd ed. New York (NY): Raven Press; 1473–97.

Baker, M.A. ; Cerniglia, G.J. and Zaman, A. ,1990. Microtiter plate assay for the measurement of glutathione and glutathione disulfide in large numbers of biological samples. Anal. Biochem., 190 : 360 – 365.

Balkan, J.; Dogru-Abbasoglu, S.; Kanbagli, O.; Cevikbas, U.; Aykac-Toker G. and Uysal, M. ,2001. Taurine has a protective effect against thioacetamide-induced liver cirrhosis by decreasing oxidative stress. Hum Exp Toxicol., 20: 251-254

Birdsall, T.C. ,1998. Therapeutic applications of taurine. Altern Med Rev. Apr., 3:128-36.

Buyukberber, M.; Cemil Savaş, M.; Bagci, C. Koruk, M.; Murat, T. G.; Ediz, T.; Tugba B., Nurdan ,Ö .C.,2009. Therapeutic effect of caffeic acid phenethyl ester on cerulein-induced acute pancreatitis. World J Gastroenterol, 15: 5181-518.

Byung , I. C.; Ah, Y. K.and Joon, K. H., 2001. Hepatobiliary and pancreatic: Unusual pancreatic lesions. Journal of Gastroenterology and Hepatology,14: 827.

Camargo, E.A.;Esquisatto, L.C. and Esquisatto, M.A. ,2005. Characterization of the acute pancreatitis induced by secretory phospholipases A2 in rats. Toxicon. 2005; 46:921Y926.

Cardin, V.; Segura, C. and Pasants-Morales, H., 1999. Neuro. Sci. Res., 56: 659 - 667.

Ceranowiczi , D.; Warzechai , Z. ; Dembinski, A.; Ceranowiczi, P. and Cieszewska, J.,2010. Role of hormonal axis, growth hormone- IGF-1, in therapeutic effect of ghrelin in the course of cerulean-induced acute pancreatitis. Journal of Physiology and Pharmacology, 61: 599-606.

Chattopadhyay, K. ; Biswas, U. and Banerjeen, R. K., 2004. Turmeric and curcumin: biological actions and medicinal applications. Curr Sci., 87:44-50.

Chen, Y.; Li, S. and Zhang, X., 1999. Taurine inhibits deposition of extracellular matrix in experimental liver fibrosis in rats Zhonghua Ganzangbing Zazhi., 7: 165-167.

Chen, A .; Xu , J . and Johnson, C . ,2006. Curcumin inhibits human colon cancer cell growth by suppressing gene expression of epidermal growth factor receptor through reducing the activity of the transcription factor Egr-1. Oncogene 25; 278-87.

Cheng, A.L.; Hsu, C.H.; Lin, J.K.; Hsu, M.M.; Ho, Y.F.; Shen, T.S.; Ko, J.Y.; Lin, J.T.; Lin, B.R.; Ming-Shiang, W.; Yu, H.S.; Jee, S.H.; Chen, G.S.; Chen, T.M.; Chen, C.A.; Lai, M.K.; Pu, Y.S.; Pan, M.H.; Wang, Y.J.; Tsai, C.C. and Hsieh, C.Y. ,2001. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions, Anticancer Res., 21: 2895–2900.

Chiba, Y.;Ando, K. and Fujita, T., 2002. The protective effects of taurine against renal damage by salt loading in Dahl salt-sensitive rats. J Hypertens ; 20: 2269-2274

Dervenis, C.; Johnson, C.D.; Bassi ,C.; Bradley,E.L.;Imrie, C.W. McMahon, M.J.and Modlin, I. ,1999. Diagnosis, objective assessment of severity and management of acute pancreatitis. The Santorini Consensus Conference. Int J Pancreatol , 25:195-210.

Devasagayam, T.P.A. and Tarachand, V. ,1987. Decreased lipid peroxidation in the rat kidney during gestation. Biochem. Biophys. Res. Commun., 145 : 134 - 138.

Ebrahim ,A.S.; Babu, E.; Thirunavukkarasu, C.and Sakthisekaran D., 2001. Protective role of vitamin E, 2-deoxy-D-glucose, and taurine on perchloroethylene induced alterations in ATPases. Drug Chem Toxicol.; 24:429-37.

Ethridge, R.T.; Chung, D.H.and Slogoff, M., 2002. Cyclooxygenase-2 gene disruption attenuates the severity of acute pancreatitis and pancreatitis-associated lung injury. Gastroenterology, 123: 1311Y1322.

Frebourg,T.; Bercoff, E., Manchon, N.; Senant.;J.; Basuyau, J.P.; Brebourg, P.; Janvresse, A.; Brunelle, P. and Bourreille. J., 1988. The evaluation of CA 19-9 antigen level in the early detection of pancreatic cancer. A prospective study of 866 patients. Cancer; 62:2287-2290.

Galli-Taliadoros, L.A.;Sedgwick , J.D.and Wood, S.A.,1995. Gene knock-out technology: a methodological overview for the interested novice. J Immunol Methods. 181.

Garber, M. and Wulff K., 1987. A New Pancrease Specific Alpha-Amylase Assay Using the Synergistic Action of Two Different Monoclonal Antibodies. Clin. Chem. 33:997.

Gibson,T.; Frederic ,T. Barrows,T. ; April M.; Katherine,A. ;Johansen , E. and Brian, S., 2007. Supplementation of taurine and methionine to all-plant protein diets for rainbow trout (Oncorhynchus mykiss). Aquaculture, 269 . 514–524

Gold, P., and Freedman, S. 0. ,1965a. Demonstration of tumorspecific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. J. exp. Med., 121:439-462.

Gold, P., and Freedman, S. 0. ,1965b. Specific carcinoembryonic antigens of the human digestive system. J. Exp. Med., 122: 467-481.

Gorelick, F.S. and Jamieson, J.D.,1994. The pancreatic acinar cell: structure-function relationships. In: Johnson LR, Alpers DH, Christensen J, Jacobson ED, Walsh JH, editors. Physiology of the gastrointestinal tract. 3rd ed. New York (NY): Raven Press; 1353–76.

Gordon, R.; Shaked, A. and Solana, D. ,1986. Taurine portects hamaster bronchioles from acute NO2-induced alteration. Am. J. Pathol., 125:585-600.

Gukovsky, I., Reyes, C.N., Vaquero, E.C., Gukovskaya, A.S., and Pandol, S.J. ,2003. Curcumin ameliorates ethanol and nonethanol experimental pancreatitis, Am. J. Physiol. Gastrointest. Liver Physiol., 284: G85–95.

Gulcubuk, A.; Altunatmaz, K. ; Sonmez, K.; Haktanir-Yatkin, D. ; Uzun, H. ; Gurel, A.and Aydin, S.,2006. Effects of curcumin on tumour necrosis factor-alpha and interleukin-6 in the late phase of experimental acute pancreatitis. J Vet Med A Physiol Pathol Clin Med., 53:49-54.

Gultekin, F.A.; Kerem, M.; Tatlicioglu, E.; Aricioglu, A.; Unsal, C.and Bukan ,N.,2007. Leptin treatment ameliorates acute lung injury in rats with cerulein-induced acute pancreatitis.World J Gastroenterol., 13:2932-8.

Hansen, S.H.; Andersen, M.L.; Birkedal, H.; Cornett, C. and Wibrand, F., 2006. The important role of taurine in oxidative metabolism. Adv Exp Med Biol.;583:129-35.

Hammarström, S.; Olsen, A.; Teglund, S. and Baranov, V., 1998.The nature and expression of the human CEA family: In Cell Adhesion andCommunication Mediated by the CEA Family: Basic and Clinical Perspectives. vol. 5 (ed. C. P. Stanners), pp. 1-30.

Heibashy, M.I.A. and El-Nahrawy, W. A.M. ,2008. Role of Taurine, Oxygen Therapy and their Mixture as Anti-cancer Agents on the N-nitrosodiethylamine (NED) Induced Cancer in Male Adult Rats. Bull. Egypt. Soc. Physiol. Sci., 28: 45-60.

Heibashy, M.I.A. and Sharoud, M.N.M. ,2008. Attenuation of the Disruptive Effects Induced by γ-Irradiation in Rats Using Ozonated Water and/or Taurine. Isotope & Rad. Res., 40: 1527-1541.

Hietaranta A, Kemppainen E, Puolakkainen P., 1999. Extracellular phospholipases A2 in relation to systemic inflammatory response syndrome (SIRS) and systemic complications in severe acute pancreatitis. Pancreas.; 18:385Y391.

Hong, J.; Bose, M.; Ju, J. ; Ryu, J. H. ; Chen, X.; Sang, S. ; Lee, M. J. and Yang, C. S. , 2004. Modulation of arachidonic acid metabolism by curcumin and related beta-diketone derivatives: effects on cytosolic phospholipase A(2), cyclooxygenases and 5-lipoxygenase. Carcinogenesis, 25: 1671-9.

Hong, R. L.; Spohn, W. H. and Hung, M. C. ,1999. Curcumin inhibits tyrosine kinase activity of p185neu and also depletes p185neu. Clin Cancer Res., 5:1884-91.

Huxtable, R.J., 1992. Physiological actions of taurine. Physiol Rev .; 72: 101-163

Ishida, J., Ohtsu, H., Tachibana, Y., Nakanishi, Y., Bastow, K.F., Nagai, M., Wang, H.K., Itokawa, H. and Lee, K.H. ,2002. Antitumor agents, part 214: synthesis and evaluation of curcumin analogues as cytotoxic agents, Bioorg. Med. Chem., 10: 3481–3487.

Jiao, Y. ; Wilkinson, J. t. ;Christine Pietsch, E. J., Buss, L.; Wang W.; Planalp, R. ; Torti , F. M. and Torti, S. V. ,2006. Iron chelation in the biological activity of curcumin. Free Radic Biol Med., 40: 1152-60.

Johnson, B.G.; J. Schlom, A.J. Peterson, J. ;Bennett, J.L. and Magnani, D. ,1986. Analysis of a human tumor-associated glycoprotein (TAG 72) identified by monoclonal antibody B72.3. Cancer Res., 46:850–857.

Johansson, C.; Nilsson, O.; Baeckström, D.; Jansson, E.-L. and Lindholm, L. ,1991. Novel Epitopes on the CA50-Carrying Antigen: Chemical and Immunochemical Studies, Tumor Biol., 12: 159-179.

Johansson, C.; Nilsson, O. and Lindholm, L., 1991. Comparison of Serological Expression of Different Epitopes on the CA50-Carrying Antigen CanAg, Int. J. Cancer, 48: 757-763.

Kawa, S.;Tokoo, M.; Hasebe, O.; Hayashi, K. ;Imai, H.; Oguchi, H.; Kiyosawa, K.; Furuta, S. and Homma, T. ,1994. Comparative study of CA_{242} and $CA_{19.9}$ for the diagnosis of pancreatic cancer, Br. J. Cancer, 70: 481-486.

Kelsen, D.P.; Daly, J.M.; Levin, B.; Kern, S.E. and Tepper, J.E., 2002. Gastrointestinal Oncology : Principles and Practice. 2nd ed. Lippincott Williams and Wilkins, A Wolters Kluwer Company, Philadelphia, Baltimore, New York, London, Buenos Aires. Hong Kong Sydney Tokyo.

Kendler, B.S., 1989. Taurine: an overview of its role in preventive medicine. Prev Med., 18:79-100.

Kihara, Y.; Yoshikawa, H. and Honda, H., 2005. Natural disruption of group 2 phospholipase A2 gene protects against choline-deficient ethionine-supplemented diet-induced acute pancreatitis and lung injury. Pancreas.; 31:48Y53.

Kim, J. H. ; Xu, C. ; Keum, Y. S. ; Reddy, B. A., 2006. Conney and A. N. Kong, Inhibition of EGFR signaling in human prostate cancer PC-3 cells by combination treatment with beta-phenylethyl isothiocyanate and curcumin. Carcinogenesis, 27: 475-82.

Klug, T.L.; Sattler, M.A.; Colcher, D. and Schlom, J., 1986. Monoclonal antibody immunoradiometric assay for an antigenic determinant (CA 72) on a novel pancarcinoma antigen. Int. J. Cancer, 38:661–669

Kloppel, G. and Maillet, B .,1993. Pathology of acute and chronic pancreatitis. Pancreas;8:659-70.

Kouri, M.; Pyrhonon, S. and Kuusela, P.,1992. Elevated CA 19-9 as the most significant prognostic factor in advanced colorectal carcinoma. J. Surg. Oncol .; 49:78-85.

Kumar, A.P., Garcia, G.E., Ghosh, R., Rajnarayanan, R.V., Alworth, W.L. and Slaga, T.J., 2003. 4-Hydroxy-3-methoxybenzoic acid methyl ester: a curcumin derivative targets Akt/NF kappa B cell survival signaling pathway: potential for prostate cancer management, Neoplasia, 5: 255–266.

Lan, M.S.; R.C. Bast, M.I. ; Colnagi, R.C. ;Knapp, D. ; Colcher, J. ; R.S. and Megzgar, R.S.,1987. Co-expression of human cancer-associated epitopes on mucin molecules. Int. J. Cancer, 39:68–72.

Lal, B.; Kapoor, A.K.; Agrawal, P.K.; Asthana, O.P. and Srimal, R.C. ,2000. Role of curcumin in idiopathic inflammatory orbital pseudotumours, Phytother. Res., 14 : 443–447.

Lantz, C. ; Chen, G. J. ; Solyom, A. M. ; Jolad S. D. and Timmermann, B. N. ,2005. The effect of turmeric extracts on inflammatory mediator production. Phytomedicine, 12: 445-52.

Lee, S.; Nicholls, J. and Park, H., 1992. Biliary sludge as a cause of acute pancreatitis. New Engl J Med.; 27:589-593.

Lee, H.S. ,2000. Water immersion stress induces heat shock protein 60 expression and protects against pancreatitis in rats. Gastroenterology, 119:220-229.

Lee, Y. H.; Im, H. H.; Jung, J. H. ;Kim, J. O.; Park, K.; Kim, W. S.; Kim, J. S.; Ahn, C. W.; Jung, Y. S.; Park, W.; Kang K., and Park, K. ,2005. Curcumin inhibits interferon-alpha induced NF-kappaB and COX-2 in human A549 non-small cell lung cancer cells. Biochem Biophys Res Commun., 334: 313-8.

Lerch,.M and Adler, G.,1994. Pathophysiology of Acute Pancreatitis. Dig Surg.;11:186-192.

Lin, J.; Pan, M. and Lin-Shiau,S., 2000. Recent studies on the biofunctions and biotransformations of curcumin. BioFactors,13:153-158

Lott, J.; Patel, S.; Sawhney, A.; Kazmierczak, S.and Love, J.,1986. Assays of serum lipase: Analytical and clinical considerations. Clin Chem;32:1290-1302.

Lowe, M.E.,1994. The structure and function of pancreatic enzymes. In: Johnson LR, Alpers DH, Christensen J, Jacobson ED, Walsh JH, editors. Physiology of the gastrointestinal tract. 3rd ed. New York (NY): Raven Press; 1531–42.

Makela, A.;Kuusi, T. and Nuutinen, P.(1999): Phospholipase A2 activity in body fluids and pancreatic tissue in patients with acute necrotizing pancreatitis. Eur J Surg. 165:35Y42.

Malo, A.;Kruger, B.; Seyhun, E.; Schafer, R.; Hoffmann, T.; Goke, B. And Kubisch, H.(2010): Taurousodeoxycholic acid reduces endoplasmic reticulum stress,trypsin activation, and acinar cell apoptosis while increasing secretion in rat pancreatic acini. Am. J. Physiol Gastrointest Liver Physiol ., 299(4) : 877-886.

Messina, S.A.and Dawson, R. J.r.(2000): Attenuation of oxidative damage to DNA by taurine and taurine analogs. Adv Exp Med Biol; 483: 355-367.

Milton, J.S.; Corbert,J.J. and Teer, P.M. (1986): Introduction to statistics 3rded . D.C.Health and Company, Cannada

Montgomery, R.C.; Hoffman, J.P.; Riley, L.B.;Rogatko, A.; Ridge, J.A. and Eisenberg, B.L.(1997): Prediction of recurrence and survival by post-resection CA 19-9 values in patients with adenocarcinoma of the pancreas. Ann Surg Oncol 1997; 4(7):551-556.

Naito, M.; Wu, X.; Nomura, H.; Kodama, M.; Kato, Y. and Osawa, T. (2002): The protective effects of tetrahydrocurcumin on oxidative stress in cholesterol-fed rabbits, J. Atheroscler. Thromb., 9 (5): 243–250.

Nevalainen, T. J; Haapamaki, M. M.; Gronroos, J.M.(2000):Roles of secretory phospholipases A(2) in inflammatory diseases and trauma. Biochim. Biophys Acta.; 1488.

Niederau, C.; Niederau, M.; Luthen, R.; Strohmeyer, G.; Ferrell, I.D. (1990): pancreatic exocrine secretion in acute experimental pancritis. Gastroenterology, 99:1120-1127.

Nilsson, O.; Johansson, C.; Glimelius, B.; Persson B.;Nørgaard-Pedersen, B.; Andrén-Sandberg, Å. and Lindholm L. (1992): Sensitivity and speciicity of CA242 in gastro-intestinal cancer. A comparison with CEA, CA50 and CA19.9. Br J Cancer 65, 215-221.

Obinata, K.; Maruyama, T.; Hayashi , M; Watanabe, T. and Nittono, H.(1996): Effect of taurine on the fatty liver of children with simple obesity. Adv Exp Med Biol .; 403: 607-613 .

Ozturk, M.; Mas, M.R. ; Yasar, M.; Akay, C.; Aydogan, H.; Deveci, S.; Comert, B.; Simsek, I.; Mas, N.; Kocar, I.H.(2003): The role of inducible nitric oxide synthase inhibitor, meropenem, and taurine in experimental acute necrotizing pancreatitis. Pancreas; 26: 357-362

Olsen, R.L. and Little, C. (1983): Purification and some properties of myeloperoxidase and eosinophil peroxidase from human blood. Biochem. J. 209(3): 781-787.

Pastor ,C.M.and Frossard, J.L.(2001): Are genetically modified mice useful for the understanding of acute pancreatitis?. FASEB J; 15:893-7.

Paterson, A.j.; Schlom, H.F.; Sears, J. and Colcher. D.(1986): A radioimmunoassay for the detection of a human tumor-associated glycoprotein (TAG 72) using monoclonal antibody B72.3. Int. J. Cancer 37 (5):659–666.

Pezzilli, R.; Fantini, L. an Maria, A. (2006): New Approaches for the Treatment of Acute Pancreatitis. JOP. J Pancreas; 7(1):79-91.

Pietrangelo, A. (1996) : Metals, oxidative stress, and hepatic fibrogenesis. Semin Liver Dis., 16: 13-30

Piper, J.T.; Singhal, S.S.; Salameh, M.S.; Torman, R.T., Awasthi, Y.C. and Awasthi, S. (1998): Mechanisms of anticarcinogenic properties of curcumin: the effect of curcumin on glutathione linked detoxification enzymes in rat liver, Int. J. Biochem. Cell. Biol., 30 (4), 445–456.

Prasad, N. S. ; Raghavendra, R.; Lokesh , B. R. and Naidu, K. A. (2004): Spice phenolics inhibit human PMNL 5-lipoxygenase. Prostaglandins Leukot Essent Fatty Acids 70; 521-8.

Rock, C.L.; Jacob, R.A. and Bow en, P.W. (1996): Up data on the biological characteristics of the antioxidant micronutrients: vitamin C, vitamin E and the carotenoids. J. Am. Diet. Ass., 96(7)32-38.

Rao, C.V.; Rivenson, A.; Simi, B. and Reddy, B.S. (1995): Chemoprevention of colon carcinogenesis by dietary curcumin, a naturally occurring plant phenolic compound, Cancer Res., 55(2): 259–266.

RefikMas, M.; Comert, B.;, Oncu, K.; Vural, S.A.; Akay, C.; Tasci, I.; Ozkomur, E.; Serdar, M.; Mas, N.; Alcigir, G. and Yener N.(2004): The effect of taurine treatment on oxidative stress in experimental liver fibrosis. Hepatol Res; 28: 207-215.

Rinderknecht, H. (1994): Pancreatic secretory enzymes.In:Gandner, J.D. et.al.The pancrease :Biology.Pathology, and disease.2 nd. Ed. New York p: 219-251.

Ruddon, R.W. (1996): Cancer Biology 3rd Ed. Oxford University Press.

Safi,F.; Schlosser,W.;Falkenreck,S.; Berger, H.G.(1996): CA 19-9 serum course and prognosis of pancreatic cancer. Int. J. Pancreatol .1996; 20(3):155-161.

Schafer, C.; Tietz, A.B.and Goke, B. (2005):Pathophysiology of acute experimental

pancreatitis: lessons from genetically engineered animal models and new molecular approaches. Digestion.;71.

Schoenberg, M.H.; Buchler, M.; Younes, M.; Kirchmayr, R.; Bruckner,U.B. and Beger, H.G.(1994) :Effect of antioxidant treatment in rats with acute hemorrhagic pancreatitis.Dig Dis Sci 1994; 39:1034-40.

Schrader , H.; Menge, B.A.; Belyaev, O.; Uhl ,W.; Schmidt, W.E.and Meier J.J.(2009): Amino acid malnutrition in patients with chronic pancreatitis and pancreatic carcinoma. Pancreas. 38(4):416-21.

Schulz ,H.U.and Niederau, C.(1994): Oxidative stress-induced changes in pancreatic acinar cells: insights from in vitro studies. Hepato-Gastroenterol; 41:309–312.

Smith, P. C.; Santibanez , J. F.; Morales, J. P. and Martinez, J. (2004): growth factor stimulates urokinasetype plasminogen activator expression in human gingival fibroblasts. Possible modulation by genistein and curcumin. J .Periodontal .Res .,39; 380-7.

Snedecor, G.W. and Cochran, W.G. (1982): Statistical Methods 7th Ed. Iowa State University Press. Am., Iowa, USA.

Solomon, T.E.(1994): Control of exocrine pancreatic secretion. In: Johnson LR, Alpers DH, Christensen J, Jacobson ED, Walsh JH, editors. Physiology of the gastrointestinal tract. 3rd ed. New York (NY): Raven Press; p. 1499–529.

Soni, K.B., Rajan, A., and Kuttan, R. (1992): Reversal of aflatoxin induced liver damage by turmeric and curcumin, Cancer Lett., 66 (2): 115–121.

Song, A.M.; Bhagat, L.and Singh, V.P.(2002): Inhibition of cyclooxygenase-2 ameliorates the severity of pancreatitis and associated lung injury. Am J Physiol Gastrointest Liver Physiol. , 283:G1166YG1174.

Svegliati Baroni, G.; D'Ambrosio, L.;Ferretti ,G.; Casini, A.; Di Sario, A.; Salzano, R.; Ridolfi, F.; Saccomanno, S.; Jezequel, A.M. and Benedetti A.(1998): Fibrogenic effect of oxidative stress on rat hepatic stellate cells. Hepatology; 27: 720-726

Sweiry, J.H. and Mann, G.E.(1996): Role of oxidative stress in the pathogenesis of acute pancreatitis. Scand J Gastroenterol Suppl 1996; 219:10-5.

Tasci, I.; Mas, M.R.; Vural, S.A.; Deveci, S.; Comert, B.; Alcigir, G.; Mas, N.; Akay, C.; Bozdayi, M.; Yurdaydin, C.; Bozkaya, H.; Uzunalimoglu, O.; Isik, A.T.and Said, H.M.(2007):Pegylated interferon-alpha plus taurine in treatment of rat liver fibrosis. World J Gastroenterol; 13: 3237-3244

Tasci, I; Mas, N.; Mas, M.R.; Tuncer, M. and Comert, B.(2008) : Ultrastructural changes in hepatocytes after taurine treatment in CCl4 induced liver injury. World J Gastroenterol .,21; 14(31): 4897-4902

Thomas, J.H. and Gillham, B. (2000): Carcinogenesis. In: Wills Biochemical Basis of Medicine. 2nd ed. London Boston Singapore Sydney Toronto Wellington. Pp. 477 - 538.

Thompson, J. & Zimmerman, W. (1988) :Tumor Biol. 9, 63-83

Tomita, Y.; Kuwabara, K.andFurue S.(2004): Effect of a selective inhibitor of secretory phospholipase A2, S-5920/LY315920Na, on experimental acute pancreatitis in rats. J.Pharmacol .Sci.; 96:144Y154.

Toouli, J.; Brooke-Smith, M.; Bassi ,C.; Carr-Locke, D.; Telford, J.and Freeny, P. (2002): Guidelines for the management of acute pancreatitis. J Gastroenterol Hepatol; 17(Suppl):S15-39.

Tunstall, R. G. ; Sharma, R. A. ; Perkins, S. ; Sale, S. ; Singh, R. ; Farmer, P. B. Steward, W. P. and Gescher, A. J.(2006): Cyclooxygenase-2 expression and oxidative DNA adducts in murine intestinal adenomas: modification by dietary curcumin and implications for clinical trials. Eur J Cancer 42; 415-21.

Uhl, W.; Schrag, H.J. and Schmitter ,N.(1997: Pathophysiological role of secretory type I and II phospholipase A2 in acute pancreatitis: an experimental study in rats. Gut.;40.

Uomo, G.;Pezzilli, R.; Cavallini ,G.(1999): Management of acute pancreatitis in clinical practice. ProInf - A.I.S.P. Study Group. Progetto Informatizzato Pancreatite Acuta. Associazione Italiana Studio Pancreas. Ital J Gastroenterol Hepatol , 31:635-42.

Ursini, F.; Maiorino, M. and Gregolin, C. (1985): The selenoenzyme phospholipids hydroperoxide glutathione peroxidase. Biochim. Biophys. Acta., 839 : 62 – 70.

Von Kleist, M.; Hesse, P., and Kananeeh, S. (1996): Comparative Evaluation of Four Tumor Markers, CA_{242}, $CA_{19.9}$, TPA and CEA in Carcinomas of the Colon. Anti-cancer Research; 16: 2325-2332.

Wu, J.T., and Nakamura, R.M. (1997):Human circulating tumor markers. American Society of Clinical Pathologists, Chicago, IL. 263 pp.

Yan, W.W.; Zhou, Z.G. and Chen, Y.D. (2004): Role of COX-2 in microcirculatory disturbance in experimental pancreatitis. World J Gastroenterol. 2004; 10:2095Y2098.

Yoshikawa, T.; Naruse, S. and Kitagawa, M. (1999):Effect of a new inhibitor of type II phospholipase A2 on experimental acute pancreatitis in rats. Pancreas.; 19:193Y198.

Zhou, Z.G.; Yan, W.W.and Chen, Y.Q. (2004): Effect of inducible cyclooxygenase expression on local microvessel blood flow in acute interstitial pancreatitis. Asian J Surg.;27:93Y98.

6/27/2011