Anti-inflammatory activity and ameliorative role of curcumin and alpha-lipoic acid on L-arginine induced acute pancreatitis in rats

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ABSTRACT

This study was designed to investigate the possible anti-inflammatory effect and ameliorative role of α-lipoic acid (ALA) and curcumin (CUR) against L-arginine (L-Arg.) induced acute pancreatitis (AP) in rats. Fifty-two male albino rats were divided into four equal groups, 13 rats each. Group I (control normal group): rats received no drugs. Group II (acute pancreatitis-induced group): rats injected intraperitoneal by L-arginine (200 mg/100 g) twice at 1- hour intervals for the induction of acute pancreatitis. Group III (L-arginine induced AP +α-lipoic acid treated group): rats injected intraperitoneally with α- lipoic acid (54 mg/kg body weight) for 7 days prior to L-arginine injection followed by 3 days later. Group IV (L-arginine induced AP+ Curcumin treated group): rats orally treated with curcumin (200 mg/kg body weight) for 7 days prior to L-arginine administration followed by 3 days later after acute pancreatitis induction. The animals were decapitated 24 and 72 hours after the last dose of L-arginine. Blood samples and pancreatic tissues were collected for determination of some serum and pancreatic tissues parameters. The obtained results revealed that, while serum marker enzymes (amylase, lipase, ALT, AST) activities, IL-6, IL-10and TNF-α levels and pancreatic tissue L-MDA and nuclear factor-Kabba B (NF-κB) concentrations were significantly increased in rats with L-arginine-induced AP, serum calcium level and pancreatic tissue antioxidant enzymes (SOD, CAT, GPx) activities were significantly reduced. Interestingly, the severity of these alterations was reduced after treatment with α-lipoic acid or curcumin that exhibited pronounced improvement in the progression of pancreatitis and protection against L-Arg induced AP probably by their antioxidant and anti-inflammatory effect. These results suggest that, curcumin or α-lipoic acid may be effective in controlling acute pancreatic status, decrease oxidative stress and have an ameliorating role in reducing acute pancreatitis complications.

Key words: Acute pancreatitis, L-arginine, α-lipoic acid, Curcumin, Pro-inflammatory cytokines.

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1. INTRODUCTION

Acute pancreatitis (AP) is an inflammatory disease of the pancreas that is associated with little or no fibrosis of the gland (Fisher et al., 2010). The experimental and clinical patho-physiology of AP is poorly understood. Therefore, AP continues to be associated with significant mortality and morbidity (Bülbüller et al., 2005).

The etiology and pathogenesis of acute pancreatitis have been intensively investigated for centuries worldwide. Many causes of acute pancreatitis have been discovered, but the pathogenic theories are controversial. The most common cause of acute pancreatitis is gallstone impacting the distal common bile-pancreatic duct. The majority of investigators accept that the main factors for acute biliary pancreatitis are pancreatic hyper-stimulation and bile-pancreatic duct obstruction which increase pancreatic duct pressure and active trypsin reflux. Several factors are responsible for the AP, like alcohol, gallstones, hypercalcemia, hyperlipidemia, abdominal trauma, malignancy, drugs like steroids, sulfonamides, furosemide, thiazides, infections like mumps, coxsackie virus, ascaris and structural abnormalities like pancreas divisum (Martinez et al., 2006). Moreover, acute pancreatitis occurs when intracellular protective mechanisms to prevent trypsinogen activation or reduce trypsin activity are overwhelmed. However, little is known about the other acute pancreatitis. Pancreatic hyper-stimulation and pancreatic duct obstruction increase pancreatic duct pressure, active trypsin reflux, and subsequent unregulated activation of trypsin within pancreatic acinar cells. Enzyme activation within the pancreas leads to auto-digestion of the gland and local inflammation. Acute pancreatitis, an inflammatory disease of the

pancreas, is mild and resolves itself without serious complications in 80% of patients, but it has complications and a substantial mortality in up to 20% of patients Lund et al.,(2006). It has recently been demonstrated that excessive formation of free oxygen radicals and changes in cytokine levels might have a role in the pathogenesis of AP. Free oxygen radicals may contribute to pancreatic acinar cell damage due to ischemia reperfusion injury through consumption of antioxidants within the tissue, and also have direct toxic effects on acinar cells (Pooran et al., 2003). Several cytokines are released from damaged pancreatic cells and systemic immune cells during pancreatic inflammation. Interleukin (IL)-1 and tumor necrosis factor (TNF-α) are major cytokines that play a role in AP. In addition, IL-2, IL-6, IL-8, IL-10, and nitric oxide (NO) contribute to deterioration in the clinical condition. These cytokines lead to worsening of AP and systemic complications by increasing capillary permeability (Gukovsky et al., 1998).

L-arginine is an amino acid that is essential for creating proteins in the body; the body converts it into nitric oxide, a chemical that widens the blood vessels for better blood flow. L-arginine also helps the body release bodily substances such as insulin and growth hormone. Mizunuma et al.,(1984) were first to report that, intraperitoneal (i.p.) administration of excessive doses of L-arginine (500 mg/100 g body weight) in rats selectively damage pancreatic acinar cells without any morphological change in islets of langerhans or other organs. Based upon this observation (Tani et al., 1990) reported an L-arginine induced rat model of necrotizing acute pancreatitis. The dose used in this model was 500 mg/100 g. Doses higher than 500 mg/100 g body weight caused very high mortality. Since these observations, the model of L-arginine induced acute pancreatitis in rat has been used in different laboratories. The dose as well as frequency of administration has been varied. The different doses and frequencies of administration of L-arginine evaluated in rat by different investigators have been reviewed by Hegyi et al., (2004 and 2010).

Alpha-Lipoic Acid (ALA) is a mitochondrial fatty acid that is highly involved in energy metabolism. It is synthesized in the body and can be consumed through eating meats and minimally in some fruits/vegetables. In supplement form; it has shown benefit against various forms of oxidation and inflammation. These effects carry on to benefits that protect one from heart diseases, liver diseases, diabetes, and neurological decline with age. ALA significantly reduces morbidity and mortality by preventing organ dysfunction induced by free radicals in the pancreas (Bulut et al., 2011). α-Lipoic acid is a thiol antioxidant compound with demonstrated direct free-radical scavenging properties (Park et al., 2005, Atmaca, 2004). Treatment with alpha lipoic acid exhibited pronounced improvement in the course of pancreatitis induced by L-arginine (Abdin et al., 2010). Curcumin, which is a yellow curry pigment obtained from turmeric (*curcuma longa*), has been demonstrated to be a potent anti-inflammatory, anti-carcinogenic and antioxidant agent, and a number of pre-clinical trials has been carried out with respect to the effects of curcumin in cancer prevention and anti-inflammation (Punithavathi et al., 2000, Kim et al., 2003, Duvoix et al., 2005). Inflammatory cytokines are considered to be the fundamental systemic mediators of acute pancreatitis are responsible for the systemic complications of APC Zako et al., (2000). Accordingly, the purpose of the present study was to investigate the anti-inflammatory effect and ameliorating role of curcumin and α-lipoic acid in an experimental rat model of L-arginine induced acute pancreatitis via determination of some blood and pancreatic tissue biochemical parameters. Also, to determine whether administration of curcumin or α-lipoic acid to acute pancreatitisinduced-rats are beneficial for prevention and treatment of acute pancreatitis complications

2. MATERIALS AND METHODS

2.1. Experimental animals

Fifty two male albino rats of 4-5 weeks old and weighing 100 g. were used in the experimental investigation of this study. The rats were obtained from the Laboratory Animals Research Center, Faculty of Veterinary Medicine, Benha University. Rats were housed in separated wire mesh cages and kept at constant environmental and nutritional conditions throughout the period of experiment. The animals were fed on constant ration and fresh, clean drinking water was supplied ad-libitum. The animals were left 7 days for acclimatization before the beginning of the experiment.

2.2. Chemicals and drugs

All chemicals were of analytical grade and obtained from standard commercial suppliers. The drug and chemicals used in the present study were:

a. L-Arginine: purchased from El-Gomhouria Company for Trading chemicals and medical supplies, Egypt. L-Arg. Powder Was freshly

prepared as a solution by dissolving in 0.9 % NaCl and the PH was adjusted to 7 with 5 N HCL and injected intraperitoneal at a dose of (200 mg/100 g) twice at 1- hour intervals for the induction of acute pancreatitis (Hegyi et al., 2004).

b. Curcumin: manufactured by Fluka Co. for chemicals and purchased from El-Gomhouria Company for Trading chemicals and medical supplies, Egypt. Curcumin was freshly prepared by dissolved in 7 % DMSO solution and administered orally at a dose of 200 mg/ kg body weight (Aggrewal et al., 2003).

c. Alpha-Lipoic acid (Thiotacid) ®: thiotacid was obtained as pack of five ampoules of 10ml solution. Each ampoule contains thioctic acid (alpha lipoic acid) 300 mg. Alpha-lipoic acid (Thioctic acid) ® manufactured by EVA pharma for pharmaceuticals and Medical Apliances, Egypt. Alpha lipoic acid was injected intraperetineal in a daily dose of 54 mg/kg body weight (Gruzman et al., 2004).

2.3. Induction of acute pancreatitis

Acute pancreatitis in rats was induced by intraperitoneal administration of L-Arginine (200mg/100 g) 2 times at 1-hour intervals.

2.4. Experimental design

After acclimatization to the laboratory conditions, the animals were randomly divided into four groups (13 rats each) placed in individual cages and classified as follow:

Group I (control normal group): Rats received no drugs, served as control non- treated for all experimental groups.

Group II (acute pancreatitis-induced group): Rats injected intraperitoneal by L-arginine (200 mg/100 g) twice at 1- hour intervals.

Group III (L-arginine induced AP +α-lipoic acid treated group): Rats injected intraperitoneally with α-lipoic acid (54 mg/kgbody weight) for 7 days prior to L-arginine injection followed by 3 days later.

Group IV (L-arginine induced AP +Curcumin treated group): Rats received curcumin orally at a dose of (200 mg/kg body weight) for 7 days prior to L-arginine administration followed by 3 days later after acute pancreatitis induction.

2.5. Sampling

Random blood samples and pancreatic tissue specimens were collected from all animals groups (control and experimental groups) two times along the duration of experiment at 24 and 72 hour after induction of acute pancreatitis by L-arginine 200 mg/100 g.

Blood samples were collected by ocular vein puncture in dry, clean test tubes and allowed to clot for 30 minutes and serum was separated by centrifugation at 3000 r.p.m for 15 minute. The serum was separated by automatic pipette and received in dry strile tubes, then kept on deepfreeze at -20 C until use for subsequent biochemical analysis. All sera were analyzed for determination of the following parameters: Amylase, Lipase, Calcium, Alanine amino transferase (ALT), Aspartate amino transferase (AST), Tumor necrosis factor-alpha (TNF-α), Interleukin-6 (IL-6) and Interleukin-10 (IL-10).

The Pancreas was quickly removed from killed Rats by decapitation and cleaned by rinsing with ice-cold isotonic saline to eliminate any blood cells then blotted between 2 filter papers and quickly stored in a deep freezer at -20 °C for subsequent biochemical analysis**.** Briefly, pancreatic tissues were cut into small pieces, homogenized with a glass homogenizer in 9 volume of ice-cold 0.05 mM potassium phosphate buffer (pH7.4) to make 10% homogenates. The homogenates were centrifuged at 6000 r.p.m for 15 minutes at 4°C then the resultant supernatant were used for the determination of the following parameters: L-Malondialdehyde(L-MDA), Superoxide dismutase (SOD), Catalase (CAT), Glutathione peroxidase (GPx)**,** and nuclear factor-κB p65 (NF-κB p65).

2.6. Biochemical analysis

Serum amylase, lipase, calcium, alanine amino-transferase (ALT) and aspartate amino-transferase (AST), interleukin-6 (IL-6), interleukin-10 (IL-10) and Tumor necrosis factor-alpha (TNF-α) were determined according to the method described by Arneson and Brickell, (2007), Guilbault, (2013), Kuttner and Lichtenstein (1930), Schumann et al., (2003), Ferrari et al (2001), Chan and Perlstein, (1987) and Beyaert and Fiers (1998) respectively. Moreover, pancreatic tissue nuclear factor-κB, Catalase (CAT), Glutathione peroxidase (GPx), Superoxide dismutase (SOD) and L-Malondialdehyde (L-MDA) were determined according to the method described by Wang et al, (2016), Luck,(1974), Reddy et al (1993), Kakkar et al (1984) and Mesbah et al., (2004), respectively.

2.7. Statistical Analysis

The results were expressed as mean ± SE and statistical significance was evaluated by ANOVA using SPSS (version10.0) program followed by

the post hoc test, least significant difference (LSD). Values were considered statistically significant when $P<0.05$.

3. RESULTS

Table 1 Protective effects of ALA or Cur on some serum and pancreatic tissue biochemical parameters in L-arginine induced acute pancreatitis in rats (24 hour).

Animal groups Parameters	(Group 1) control normal	(Group 2) Acute pancreatitis	(Group 3) Acute pancreatitis+ALA	(Group 4) Acute pancreatitis+curcumin
Serum:				
Amylase(U/L)	366.85±6.88^{b}	380.33±5.49^{a}	301.33±13.04^{b}	297.0± 8.51^{b}
Lipase(U/L)	25.96± 0.81^{b}	33.09± 0.95^{a}	27.67 ± 2.85^{ab}	29.0 ± 1.16^{ab}
Calcium(mg/dl)	9.47± 0.18^{a}	7.13± 0.15^{c}	8.52± 0.06^{b}	8.15± 0.12^{b}
AST(U/L)	37.40± 0.51^{b}	42.90± 1.19^{a}	37.33±0.88^{b}	39.0± 0.58^{b}
ALT(U/L)	28.30±0.51^{b}	34.47±0.41^{a}	27.33±.088^{b}	29.67±0.88^{b}
IL- 6 (pg/ml)	107.27±3.67^{d}	134.83±0.8^{a}	117.17±1.76^{c}	126.84±0.88^{b}
IL-10 (pg/ml)	25.03±2.095^{c}	34.5±1.1^{a}	29.97±0.64^{b}	26.53±0.50^{bc}
TNF- α (pg/ml)	25.93 ± 2.12^{c}	52.77± 0.93^{a}	40.63 ± 1.24^{b}	42.20 ± 2.62^{b}
Pancreatic tissue:				
NF-κB (ng/g.tissue)	5.69± 0.13^{d}	36.33 ± 1.69^{a}	27.64 ± 0.21^{c}	30.68± 0.37^{b}
CAT(mmol/g.tissu)	1.53 ± 0.22^{a}	0.84± 0.22^{b}	1.27 ± 0.03^{ab}	0.87±0.20^{b}
GPx(ng/g.tissue)	7.04 ± 0.15^{a}	3.47 ± 0.02^{c}	5.197 ± 0.56^{b}	5.32 ± 0.17^{b}
SOD(ng/g.tissue)	74.49 ± 2.61^{a}	56.43 ± 1.58^{b}	64.25 ± 4.16^{b}	61.89 ± 1.22^{b}
MDA(mmol/g.tissue)	3.99 ± 0.30^{c}	7.09 ± 0.36^{a}	5.90 ± 0.40^{ab}	5.44 ± 0.41^{b}

Data are presented as (Mean ± S.E) S.E = Standard error. Mean values with different superscript letters in the same row are significantly different at ($P\leq0.05$).

4. DISCUSSION

Acute pancreatitis is a common clinical condition. It is a disease of variable severity in which some patients experience mild, self-limited attacks while others manifest a severe, highly morbid, and frequently lethal attack. The exact mechanisms by which diverse etiological factors induce an attack are still unclear. It is generally believed that the earliest events in acute pancreatitis occur within acinar cells. Acinar cell injury early in acute pancreatitis leads to a local inflammatory reaction. If this inflammatory reaction is marked, it leads to a systemic inflammatory response syndrome (SIRS). An excessive SIRS leads to distant organ damage and multiple organ dysfunction syndrome (MODS). MODS associated with acute pancreatitis is the primary cause of morbidity and mortality in this condition (Bhatia et al., 2005). The use of drugs with antioxidant and/or anti-inflammatory properties could be proposed as a therapeutic intervention in acute pancreatitis to improve the outcome of the disease Hardman et al., (2005). In this study L-arg.-induced acute pancreatitis in rats exhibited a significant increase in serum amylase and lipase activities after 24 hours and 72 hours after pancreatitis induction when compared with normal control group. Amylase and lipase are the most common parameters used for the diagnosis of AP. Amylase and lipase activities often elevate in case of AP, but not in parallel with the severity of pancreatitis (Steer, 2007). Similarly, Hegyi et al., (2004) establish that, serum amylase activity was significantly increased after induction of pancreatitis by L-arginine. Also, Szabolcs et al., (2006) reported that, administration of L-arginine significantly developed the acute pancreatitis

Table 2 Protective effects of ALA or Cur. on some serum and pancreatic tissue biochemical parameters in L-arginine induced acute pancreatitis in rats (72 hour).

Animal groups Parameters	(Group 1) control normal	(Group 2) Acute pancreatitis	(Group 3) Acute pancreatitis + ALA	(Group 4) Acute pancreatitis + curcumin
Serum:				
Amylase (U/L)	366.85±6.88^{b}	431.33±9.74^{a}	367.33±5.55^{b}	291.0± 9.03^{c}
Lipase(U/L)	25.96± 0.81^{b}	34.33± 0.33^{a}	29.42± 0.75^{b}	27.02± 1.77^{b}
Calcium(mg/dl)	9.47± 0.18^{a}	6.82± 0.61^{c}	8.71±0.16^{b}	8.36± 0.34^{b}
AST(U/L)	37.40± 0.51^{b}	41.08± 0.38^{a}	36.0± 1.16^{b}	37.27± 0.37^{b}
ALT(U/L)	28.30±0.51^{c}	36.33±0.65^{a}	27.17±1.04^{c}	30.17±1.16^{bc}
IL- 6 (pg/ml)	107.27±3.67^{c}	140.4±3.12^{a}	125.97±2.27^{b}	125.0±0.66^{b}
IL-10 (pg/ml)	25.03±2.095^{c}	35.43±0.91^{a}	32.17±0.88^{ab}	28.27±0.91^{bc}
TNF- α (pg/ml)	25.93 ± 2.12^{c}	76.07±3.09^{a}	46.2±1.19^{b}	40.43± 0.58^{b}
Pancreatic tissue:				
NF-κB (ng/g. tissue	5.69 ± 0.13^{d}	45.08± 0.62^{a}	33.76± 0.43^{c}	37.28± 1.06^{b}
CAT(mmol/g. tissue)	1.53± 0.22^{a}	0.497± 0.06^{b}	1.21 ± 0.41^{ab}	1.18± 0.36^{ab}
GPx(ng/g. tissue)	7.04 ± 0.22^{a}	3.53 ± 0.12^{b}	6.27 ± 0.48^{a}	5.71 ± 0.70^{a}
SOD(ng/g. tissue)	74.49±2.26^{a}	34.97± 4.28^{b}	69.37±3.46^{a}	70.58± 3.07^{a}
MDA(mmol/g. tissue)	3.99 ± 0.30^{c}	7.70 ± 0.44^{a}	5.19 ± 0.39^{b}	4.98± 0.24^{bc}

Data are presented as (Mean ± S.E) S.E = Standard error. Mean values with different superscript letters in the same row are significantly different at ($P \leq 0.05$).

characterized by raised of serum amylase and lipase activities. Lipase and amylase are mainly derived from pancreatic acinar cells; 99% is subsequently excreted in the ductal system, and <1% diffuses into the lymphatics and capillaries. In pancreatitis the permeability is markedly increased. Consecutively a higher concentration of enzymes reaches the general circulation resulting in their elevation.

In the present study, treatment with alpha-lipoic acid or curcumin to acute pancreatitis-induced group resulted in significant decrease in serum amylase activity and non-significantly lower serum lipase activity after 24 hours of pancreatitis. Also, serum amylase and lipase activities were significantly lower in alpha -lipoic acid or curcumin treated L-arginine-induced acute pancreatitis group after 72 hours of pancreatitis induction. These findings were in agreement with that obtained by Park et al., (2005) who studied the effect of ALA prior to AP although he used chole cystokinin for induction of AP. Curcumin attenuate acute pancreatitis in rodents when administered before, concomitantly to or after the instigating agent curcumin did reduce serum amylase, Lipase and IL-6 as well as bacterial translocation Shapiro et al., (2006).

It was found that amylase and lipase levels were significantly decrease in the ALA-treated group that significantly increased in cerulein- induced AP group Bulut et al., (2011). In nearly similar study statistical results of serum amylase and lipase levels of the curcumin group were found to be significantly lower in comparison with the taurocholate-induced acute pancreatitis group, with respect to all time points Gulcubuk et al., (2013). Additionally, serum amylase and lipase levels are most commonly obtained as biochemical markers of pancreatic disease, particularly AP.

Serum amylase activity has been used for many years for the evaluation of patients with acute abdominal pain and suspected pancreatic disorders. The elevation of serum pancreatic lipase levels is often considered to be the most sensitive and specific marker of AP. The serum amylase and lipase levels are commonly used as markers of AP. Therefore, we examined serum amylase and lipase activity during cerulein induced AP. The administration of *Curcuma longa* significantly reduced the serum amylase and lipase levels Seo et al., (2011).

In the current study L-Arginine-induced acute pancreatitis group showed a significant decrease in serum calcium concentration. Total calcium levels dropped significantly 30 minutes after pancreatitis was induced, ionized calcium is a more reliable indicator of calcium fluxes in acute experimental pancreatitis since it remains depressed longer than total serum calcium Izquierdo et al., (1985).

Intraperitoneal injection of α-lipoic acid or oral administration of CUR in L-arginine induced acute pancreatitis in rats caused a significant increase in serum calcium concentration when

compared with acute pancreatitis non treated group. Oxidative damage was observed by decreased serum antioxidant enzymes and calcium (Ca^{+2}) as a result of intraperitoneal injection of cyclophosphamide (CP) to induce oxidative cardiac, testicular and urotoxic damage. These CP-induced pathological and biochemical alterations were attenuated by treatment with ALA Motawi et al., (2010). In another study a diet supplemented with ALA prevented hypertension and associated abnormal biochemical and histopathological changes in fructose treated in WKY rats. It was found that.ALA may act directly on Calcium channels via DHLA to prevent oxidation of membrane sulfhydryl group leading to lowered cytosolic calcium Vasdev et al., (2000). Also, gamma-irradiated rats exhibited decrease of serum calcium concentration. Moreover, treatment of gamma-irradiated rats with the new curcumin analogues showed significant amelioration in the in-vivo antioxidant status, liver and kidney functions, as well as the anti-inflammatory markers and serum calcium El-Gazzar et al., (2016).

In the present study a significant increase in serum ALT and AST activities were observed in acute pancreatitis induced group. Similarly, Yenicerioglu et al., (2013) reported that, serum AST and ALT activities were increased markedly following the intraperitoneal injection of L-arginine solution. After acute pancreatitis induction the results revealed marked hepatic damage as evidenced by significant increase in ALT and AST activities (Emam, 2015).Increase of liver enzyme activities (ALT, AST) probably due to hepatic ischemia or hepatic damage caused by toxic products from the pancreas. Liver injury is a manifestation of the systemic inflammatory response during acute pancreatitis. The increased activities of serum AST, ALT, and ALP obviously indicated that the liver is susceptible to L-Arg. induced toxicity.

In the current study, serum AST and ALT activities were lower in the ALA-treated pancreatitis group all over the periods of the experiment when compared with acute pancreatitis non treated group. These results are nearly similar to those recorded by Abdin et al., (2010).Treatment with alpha lipoic acid exhibited pronounced improvement in the course of pancreatitis. Also, oral administration of CUR in pancreatitis induced rats resulted in significant decrease in serum AST and ALT activities. Similarly, Yu et al., (2011) found that, curcumin treatment significantly reversed the elevation of serum ALT and AST activities in AP mice.

L-arginine induced acute pancreatitis in rats resulted in significant increase in serum IL-6, IL-10 and TNF-α concentration when compared with control normal group. Several cytokines and other non-cytokine inflammatory mediators are produced rapidly during pancreatitis (Norman, 1998).This due to the initial clinical response to pancreatitis is a systemic inflammatory response (SIRS) which, if abnormally persistent, develops into a worsening scenario of tissue damage. Inflammatory cytokines are considered to be the fundamental systemic mediators of acute pancreatitis (AP) and are responsible for the systemic complications of AP. Both the TNF-α and the IL-6 levels of L-Arginine induced acute pancreatitis group were already elevated significantly at 12 h and peak at 24 h versus the control group (Czako et al., 2000).

Moreover, tumor necrosis factor (TNF)-α and IL-1β are the major cytokines released from macrophages. In addition to their cytotoxic effects, they also play a significant role in inflammatory reactions and regulation of inflammation (Steer, 2001). Neutrophils release free oxygen radicals and several lysosomal enzymes during inflammation and following trauma. TNF-α and IL-1β are also released from activated neutrophils following stimulation (Gultekin et al., 2007). Administration of IL-10 has a protective effect in animal models of sepsis. Also IL-10 administration in experimental AP leads to a reduction in both the local inflammatory response and subsequent mortality (Bahatia et al., 2000). Clinical and experimental studies have shown that, serum interleukin IL-1β, IL-6, IL-8, IL-10 and tumor necrosis factor-α (TNF-α) are increased in patients with AP (Osman et al., 2002).

Intraperitoneal injection of α-lipoic acid in L-arginine-induced acute pancreatitis in rats caused a significant decrease in serum IL-6 and TNF-α level after 24 and 72 hours of induction with a marked decrease in serum IL-10 only after 24 hours when compared with acute pancreatitis non-treated group. Serum TNF-α, IL-6 and IL-10 concentration was significantly lower in CUR treated L-arginine-induced acute pancreatitis group. α-lipoic acid reduces the serum levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6.These results indicate that, pro-infl-ammatory cytokine levels are elevated in mice treated with or without ALA despite attenuated pancreatitis Park et al., (2005). These results suggest that ALA decreases the inflammatory response by inhibiting activation and infiltration of neutrophils, which play a role in triggering tissue damage, and that ALA protects the pancreas tissue from free oxygen radical-

induced damage. This suggestion was confirmed by Bulut et al., (2011) who reported that, TNF-α and IL-1β levels were significantly lower in the ALA-treated pancreatitis group compared to the saline-treated pancreatitis group. The significant lower in serum TNF-α, IL-6 and IL-10 concentrations observed in CUR treated L-arginine-induced acute pancreatitis group are nearly similar to those recorded by Kim et al., (2003) who reported that, two enzymes involved in inflammation. The anti-inflammatory action of curcumin seems to be closely related to the suppression of pro-inflammatory cytokines and mediators of their release such as TNF-γ, IL-Iβ, and nitric oxide synthase. Curcumin was determined to reduce TNF-α and IL-6 serum levels in the late phase of AP (Gulcubuk et al., 2006).

A significant increase in pancreatic tissue NF-κB level was observed in L-Arg. induced acute pancreatitis in rats when compared with the normal control group. These results are nearly similar to those recorded by Rakonczay et al., (2007) who reported that, nuclear factor κB (NF-κB), has been shown to play a critical role in the development of acute pancreatitis. Reactive oxygen species (ROS), generated by infiltrating neutrophils, are considered as an important regulator in the pathogenesis and development of pancreatitis. A hallmark of the inflammatory response is the induction of cytokine gene expression, which may be regulated by oxidant-sensitive transcription factor, nuclear factor-kappaB (NF-κB). O'Reilly et al., (2006) reported that, systemic NF-κB activation occurs in acute pancreatitis, compared to healthy controls.

Intraperitoneal injection of ALA and oral administration of curcumin to L-Arg. induced acute pancreatitis in rats exhibited a significant decrease in pancreatic tissue NF-κB concentration. Berkson et al., (2009) discuss the poly activity of ALA as an agent that reduces oxidative stress, its ability to stabilize NF-$_{\kappa}$B, its ability to stimulate pro-oxidant apoptosic activity, and its discriminative ability to discourage the proliferation of malignant cells. Moreover, Gulcubuk et al., (2013) investigate the effects of curcumin on tissue injury and pro-inflammatory cytokines in the early and late phases of AP who reported that, curcumin inhibited nuclear factor-κB (NF-κB) at all time points. The beneficial effects of curcumin are due to its ability to inhibit activation of NF-κB and AP-1 and the resulting inflammatory response, particularly the effects of curcumin on NF-κB (Gukovsky et al., 2003). Also, activation of inflammatory cells, oxidative stress together with Pro-inflammatory cytokines play the central role in the systemic inflammatory process induced by acute pancreatitis (AP).

In the current study, a significant increase in pancreatic tissue MDA concentration was observed after 24 and 72 hours of L-arginine induced acute pancreatitis in rats when compared with normal control group. Lipids are one of the major targets for free radical damage following pancreatitis. Free oxygen radicals initiate lipid peroxidation by removing one hydrogen atom from polyunsaturated fatty acids with the subsequent formation of hydroperoxides. As a result of these reactions, the membrane fluidity and membrane integrity of cells are impaired, leading to disintegration of cells and cell death. These subcellular structures that are released into the extracellular environment trigger several inflammatory events and further worsen the ongoing damage (Eşrefoğlu et al., 2006).The MDA is an indicator of lipid peroxidation and cellular damage under oxidative stress Robles et al., (2015). Similarly, Biradar and Veeresh (2013) reported that, MDA a marker of lipid peroxidation was elevated in L-arginine induced acute pancreatitis in rats. Inflammatory explosion and oxidative stress are important mechanisms of injury in acute necrotizing pancreatitis and induction of ANP caused increases in pancreatic tissue malondialdehyde (MDA) concentration (Turkyilmaz et al., 2016).

The MDA level in the ALA treated acute pancreatitis induced group was found to be significantly lower compared to the non-treated acute pancreatitis group. Alpha lipoic acid respectively provided protection against L-arginine induced acute pancreatitis possibly by their antioxidant and anti-inflammatory effect. Treatment with alpha-lipoic acid exhibited pronounced improvement in the course of pancreatitis, a decrease in malondialdehyde level was observed after treatment with ALA when compared with sham group Abdin et al., (2010).In a nearly similar study oxidative stress was reduced, which was indicated by lower serum MDA content in case of administration of ALA in acute Lung injury model Bulmuş et al., (2013). Moreover, oral administration of CUR to L-Arg. induced acute pancreatitis in rats resulted in significant decrease in pancreatic tissue L-MAD level. The anti-carcinogenic effect of CUR is produced through its protective effect against oxidative damage. CUR treated rats displayed a significant decrease in MDA in Diethyl Nitrosamine Induced Hepatotoxicity in rat model Kadasa et al., (2015).

In an early similar study alpha lipoic acid provided protection against L-arginine induced acute pancreatitis possibly by their antioxidant and

anti-inflammatory effect. Treatment with alpha lipoic acid exhibited pronounced improvement in the course of pancreatitis and a decrease in malondialdehyde (MDA) level was observed after treatment with ALA when compared with sham group Abdin et al., (2010). Also, oxidative stress was reduced, which was indicated by lower serum MDA content in case of administration of ALA in acute Lung injury model Bulmuş et al., (2013)**.**Additionally, alpha-lipoic acid markedly decreased the production of malondialdehyde (MDA) and the generation of reactive oxidative species (ROS). These results indicated that treatment with alpha-lipoic acid significantly improved behavioral alterations, protected against oxidative stress, and restored central cholinergic system in the rat model of vascular dementia (Zhao et al., 2015). Furthermore, decreased MDA level was found in asthmatic animals after treatment with curcumin Shakeri et al., (2017).

A significant decrease in Pancreatic tissue CAT, GPX and SOD activities were observed after 24 and 72 hour in L-arginine induced acute pancreatitis in rats when compared with normal control group. These low levels of antioxidant enzyme gene expression may provide an explanation for the extraordinary sensitivity of pancreatic cells towards cytotoxic damage.CAT plays a significant role in the pathogenesis of inflammation including AP. In a similar study (Abreu et al., 2016) reported that, in L-arginine-induced AP model a marked decrease in CAT activity was observed in the pancreas compared with the control group. Oxidative stress has a serious role in the pathogenesis of AP. Thus, decreasing of oxidative stress may prevent induction and progression of AP. Free radical scavengers, CAT and SOD provide significant protection in pancreas. SOD removes superoxide radical by converting it into H_2O_2 that is rapidly converted to water by CAT. Therefore, any alteration in the activity of these enzymes may result in a number of deleterious effects due to accumulation of superoxide radicals and hydrogen peroxide kilic et al., (2016). Furthermore, Jaworek et al., (2016) reported that, a significant decrease in GPx activity was observed in the pancreas of AP induced rats. Also, GPx of acute pancreatitis rats was significantly decreased compared to the sham group (Sit et al., 2014).As described by Abu-Hilal et al., (2006)who observed that, the mean values of SOD activity was found to decrease in patients with acute pancreatitis.SOD inhibitor diethyldithiocarbamate can cause pancreatic fibrosis and can be used as a rodent model for the development of pancreatic fibrosis from the viewpoint of oxidative stress(Girish et al., 2011).In a similar study Mirmalek et al., (2016) found that, pancreatic SOD activity in pancreatitis models, that induced using L-arginine, was decreased in a comparison with control non treated group.

In the present study, alpha-lipoic acid and curcumin treated L-Arg. induced acute pancreatitis in rats resulted in a significant increase in pancreatic tissue GPX and SOD activities after 72 hour while CAT activity was non-significantly increased when compared with pancreatitis-induced non treated group. Various studies have indicated the antioxidant effects of ALA and its reduced form dihydrolipoic acid. Similarly, Dincer et al., (2002) reported that, SOD was reduced as a result of diabetes and using of ALA improved and increase SOD activity. The impact of a bioavailability enhanced preparation of curcuminoids on the biomarkers of systemic oxidative stress in patients with solid tumors receiving standard chemotherapy regimens was reported by (Panahi et al., 2014).They noted a decrease in SOD activity in inflammable cells and supplementation with curcuminoids was associated with a significantly greater elevation in the activity of SOD associated with a significant improvement of systemic oxidative stress.Also, It was determined that the increased activity of CAT as a result of the examination of the α-LA treated samples, are likely caused by the strong antioxidant properties of α-LA and its restorative effect on endogenous antioxidants. These findings suggest that α-LA exerts preventive effects only if it is administered prior to the induction of an injury (Bulmus et al., 2013).

Cellular antioxidant enzymes are one of the most directly acting molecules that counteract oxidative burst no matter how that is generated in the system. Ghosh et al., (2015) showed that, there is a decrease in the antioxidant enzyme activities in the hepatic tissues of streptozotocin-induced diabetic rats and CUR administration restored those enzyme activities towards the normal value by counteracting reactive oxygen species. Glutathione peroxidase (GPx) plays an important role in the metabolism of hydrogen and lipid peroxides by using reduced glutathione. Treatment with alpha lipoic acid (ALA) significantly inhibited spinal cord ischemia/reperfusion lipid peroxidation, and maintained cellular GPx causing elevating in GPx activity (Somi et al., 2013). GPx which consider the key enzymes in elimination of free radicals, the anti-carcinogenic effect of CUR is produced through its protective effect against oxidative damage and its antioxidant property exerting as a powerful scavenger for oxygen free

radicals and its ability to increase intracellular glutathioneperoxidase (GPx) activity (Kadasa et al., 2015). Moreover, treatment with curcumin in gastritis-induced rats resulted in a significant increase in GPx activity (Hussein et al., 2016).

5. CONCLUSION

In conclusion, the present study suggests that treatment with curcumin or α-lipoic acid significantly ameliorated the severity of L-arginine-induced acute pancreatitis in rats by inflammatory mediators and oxidative stress markers and this effect may be due to the strong antioxidant and anti-inflammatory properties of curcumin and α-lipoic acid. We recommended that, administration of curcumin or α-lipoic acids are very important for protection of pancreatic tissue against oxidative stress andpreventing organ dysfunction induced by free radicals in the pancreas

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