ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

Potential Anti-inflammatory Effect of Telmisartan In Experimentally Induced Acute Pancreatitis in Rats.

SAMIA M. M. ELSHIATY[1], HANAN T. EMAM[2], THANAA BELAL[3]

1, 2.Department of Pharmacology, Faculty of Medicine, Benha University, Egypt.
3. Department of Biochemistry, Faculty of Medicine, Benha University, Egypt.

Manuscript Info

Manuscript History:

Received: 12 April 2014
Final Accepted: 23 May 2014
Published Online: June 2014

Key words:
Acute pancreatitis (AP) - Peroxisome proliferators activated receptor (PPARs) - Thiazolidinediones (TZDs) - Rosiglitazone (Ros)- ***Telmisartan (Tel).***

Corresponding Author
HANAN T. EMAM

Abstract

Background: Acute pancreatitis (AP) is an acute inflammatory disorder of the pancreas. The destruction of pancreatic parenchyma induces a systemic activation of coagulation, kinin, complement and fibrinolytic cascades with liberation of cytokines and reactive oxygen metabolites.
Peroxisome proliferator–activated receptors (PPARs) play key roles in the processes of fat metabolism, adipocyte differentiation, tumorigenesis, inflammation and variety of immune processes. Telmisartan is the only angiotensin receptor blocker (ARB) that may modulate PPARγ activation at physiologic plasma concentrations. Telmisartan may reduce markers of inflammation, such as interleukin-6 and C-reactive protein, oxidative stress and improves markers of vascular function.

The aim of the current article was to investigate the possible anti-inflammatory, antioxidant effects, and peroxisome proliferator-activated receptor-γ (PPARγ) properties of the angiotensin type 1 receptor blocker telmisartan in experimentally induced acute pancreatitis.

Materials and Methods:Fifty male albino rats were divided randomly into 5 groups; control normal group and 4 acute pancreatic groups group (n=40). Acute pancreatitis were induced by i.p. injection of 20% L-arginine hydrochloride in saline (2x250 mg/100 g at 1 h interval) and subdivided equally into acute pancreatic group (no treatment); AP treatedt with Tel or Ros alone or their combination groups. Serum amylase and lipase activity were determined. Also TNF-α, IL-6, MDA and CAT were estimated in addition to histopathological examination.

Results: Ros alone or in combination with Tel induced significant attenuation of serum amylase and lipase activity. Also TNF-α, IL-6, MDA and CAT were improved. While Tel induced insignificant improvement of previous parameters

Conclusion: Use of rosiglitazone associated with a reduced risk of AP by improving inflammatory status and oxidative stress reflecting the important role of PPAR-γ in AP. Furthermore, telmisartan does not ameliorate acute pancreatic inflammation. Both agents have affinity for PPAR-γ, telmisartan binds to the receptor in a different manner, resulting in distinct pharmacological actions.

INTRODUCTION

Acute pancreatitis (AP) still remains an enigmatic clinical problem. No specific treatment is available to treat AP. Many therapies and medical management is aimed to control the sign and symptoms of AP, using steroids, analgesics and anti-inflammatory agents. These compounds are very expensive and not reliable. Hence, there is need of potential antioxidant & anti-inflammatory agents which are cost effective and have several advantages than the others [1].

Acute pancreatitis (AP) can sometimes, though not always, is a life-threatening disease with a significant impact on patient health. Up to 25% of patients with AP suffer a severe form which accounts for the high mortality rate of AP[1,2]. Autoactivation of digestive enzymes in the pancreatic acinar cells and the subsequent destruction of pancreatic parenchyma induces a systemic activation of coagulation, kinin, complement and fibrinolytic cascades with liberation of pro- inflammatory cytokines, such as interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α) and reactive oxygen metabolites. In addition, micro- circulatory disturbances and leukocytes activation play a crucial role in development of AP and its associated serious sequels [3,4,2].

The Peroxisome proliferators activated (PPAR) family consists of at least three different isoforms; PPARα, PPARδ , PPARγ[5]. The modulatory role of PPAR receptor has been proposed in the inflammatory response of different organs [6].

PPARγ is a member of the nuclear hormone receptor superfamily originally reported to be expressed at high levels in adipose tissue and to play a critical role in adipocyte differentiation, glucose metabolism, lipid storage and suppress inflammatory gene expression [7,8].

PPARγ is expressed in both endocrine and exocrine pancreatic cell types [9] . Its role in pancreas is not restricted to insulin signaling pathway, it has been shown to be imported in cell growth, metabolism (in particular response to altered energy homeostasis), apoptosis and inflammation [10] .

Activation of PPARγ receptors leads to anti-inflammatory and antiproliferative effects as well as increased insulin sensitivity, improvement in dyslipidemia and regression of athrosclerosis [11].PPARγ has powerful synthetic ligands, the thiazolidinediones (TZDs) also called glitazones; torglitazone, ciglitazone, pioglitazoner, and rosiglitazone. TZDs are used to treat type2 diabetes because of their efficacy in controlling blood glucose secondary to enhancing insulin action through a mechanism (s) that is yet to be completely elucidated[12] . Currently, PPAR-γ agonists have also been found to have excellent antioxidant activity [13,14]. Newer studies have also reported that PPAR-γ agonists exhibit anti-inflammatory properties which are due to negative regulation of the expression of pro-inflammatory molecules such as interleukin-1b (IL-1b), IL-6 and TNF-α [15,16]. Considerable evidence indicates that PPARγ agonists inhibit inflammatory responses during inflammatory diseases [17,18] .

Rosiglitazone, PPARγ agonist, is a widely used drug for the treatment of type 2 diabetes mellitus. It increases insulin sensitivity of peripheral tissues. In addition, there is evidence that rosiglitazone has anti-inflammatory effects [19,20].

Telmisartan is an orally active, long-acting, non-peptide angiotensin type 1 (AT_1) receptor blocker (ARB) with high selectivity for the AT_1 receptor. Telmisartan is a potent antihypertensive drug [21].

In addition, telmisartan is the only ARB that may modulate PPARγ activation at physiologic plasma concentrations, an effect that is likely to be related to telmisartan high lipophilicity. Several studies have found that telmisartan can influence PPARγ gene expression. In treatment hypertensive patients, telmisartan treatment significantly increased PPARγ mRNA levels in peripheral monocytes [22].

Telmisartan has also been shown in animal models to reduce the levels of several markers of inflammation, such as interleukins and TNFα. In a rat model, telmisartan protected against experimental autoimmune myocarditis, partly by suppressing inflammatory cytokines and oxidative stress [23].

Despite various experimental and clinical testing of potential therapeutic drugs, no specific therapeutic strategy has been shown to be uniformly effective in controlling AP and its lethal complications. Therefore, there is a necessary need for development of more effective therapeutic alternatives.

This study aimed to determined the anti-inflammatory effect of telmisartan compared with rosiglitazone in experimental model of acute pancreatitis

MATERIALS AND METHODS

Animals:

Adult male albino rats, with initial body weight ranging from (150-200 g) were used. Rats were purchased from Experimental Animal Breeding Farm, Helwan. All animals were housed in a controlled laboratory conditions at 20-

25ºC in a 12h light /dark cycle and had free access to food and water. They were allowed for one week acclimatization period before to their use in the experiment at Pharmacology Department, Faculty of Medicine, Benha University.

Drugs and Chemicals:

- L-arginine (Sigma, USA), it was supplied as pure powder and was dissolved in sterile saline (0.9%) ,intraperitoneal (i.p.) administration .
- Rosiglitazone (Avandia; GlaxoSmithKline, USA) was administered after being suspended in 1ml of sterile saline (0.9%).
- Telmisartan (Boehringer Ingelheim, Germany) freshly prepared, was administered after being suspended in 1ml of distilled water.
- TNF-α detection ELISA kits was obtained from Biosource, Belgium.
  Drugs were given by the oral route through an orogastric catheter.

All the other chemicals used were purchased from Sigma Co., USA

Experimental groups:

Fifty male albino rats were divided randomly into 5 groups; (1)control normal group received 1ml of physiologic saline by IP injection; and 4 acute pancreatic groups Acute pancreatitis were induced by two ip injection of 20% L-arginine hydrochloride in saline (2x250 mg/100 g at 1 h interval) causes pancreatitis without mortality [24] then, subdivided equally into; (2) acute pancreatic group(no medication); (3) acute pancreatic with rosiglitazone administration group, at the dose of 10mg/kg of bw after suspended in 0.9% NaCl to the volume of 1 ml, by an orogastric catheter [25],group (4) acute pancreatic with telmisartan administration group, at the dose of 10mg/kg of bw after suspended to the volume of 1 ml of distilled water by an orogastric catheter [23] and group (5) acute pancreatic with rosiglitazone plus telmisartan administration group.
Treatment started one hour prior to induction of AP, The rats were scarified after 24 hours from AP.

Experimental Parameters and design:

At the end of the experimental period, the animals were anesthetized by ether. Blood samples were obtained from retro-orbital venous plexus using capillary pipette. The blood clot and the samples were centrifuged for 15 minutes at 3000 rpm. Sera were separated and stored at -20C until being used for determination of serum amylase (U/L) according to the method of [26] and lipase activity (U/L) according to the method of [27]. Serum tumor necrosis factor-α (TNF-α) (pg/ml) and interleukin-6 (IL-6) (pg/ml) were determined in serum using the commercially available ELISA kits according to the methods of [28] and [29] respectively. Malondialdhehyde (MDA) (nmol/ ml) as a marker of lipid peroxidation following the method described by[30] and catalase (CAT) activity (U/ml) was determined following the method described by[31].

In addition, pancreas was isolated from animal after scarification. Pancreatic tissue was stored at -80C until further examination.

Histopathological Examination:

Samples of pancreatic tissue were fixed in 10% buffered formalin solution, embedded in paraffin using standard methods, cut into 5 um sections, stained with hematoxylin-eosin, and then assessed under light microscopy and examined for grading the histopathological alterations. Pancreatic edema, leukocyte infiltration, acinar vacuolization, and necrosis were described with scores ranging from 0 to 3 (0 being normal and 3 being severe) as previously described [32, 33].

Statistical analysis:

All data were expressed as mean ±S.E.M. and analyzed with statistical package SPSS (Version 10, 2002) for Windows. One-way analysis of variance (ANOVA) was used to determine statistically significant differences among the groups, and means of every two different groups were detected with Student's t-test. $p<0.05$ was considered statistically significant.

RESULTS

In the present study, ip injections of L arginine induced acute pancreatitis as evidenced by significant increase ($P<0.05$) in serum levels of amylase and lipase (Tab.1, Fig.1, 2).

Pretreatment with rosiglitazone at the dose of 10mg/kg at the same time of induction of AP, produced marked improvement of acute pancreatitis manifested by the significant decreases ($P<0.05$) in serum levels of amylase and lipase compared with acute pancreatitis. While, there was a significant increase ($P<0.05$) in serum amylase and lipase in rosiglitazone pretreated group when compared with control group (Tab.1, Fig.1, 2).

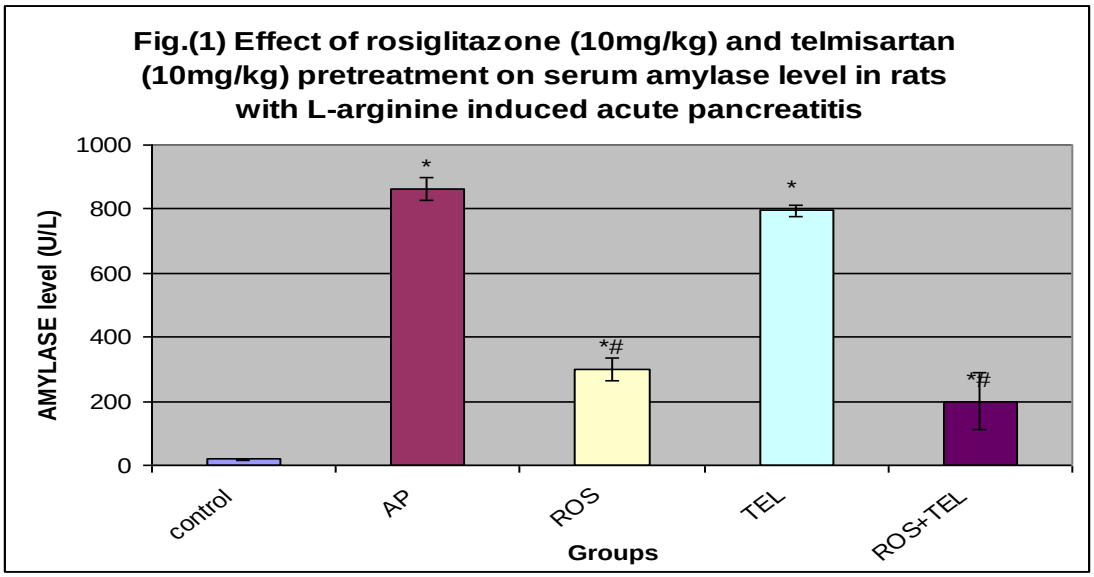
Pretreatment with telmisartan at the dose of 10mg/kg of bw produced insignificant decrease ($P>0.05$) in serum amylase and lipase level as compared to AP group. While, there was a significant increase ($P<0.05$) in serum amylase and lipase in telmisartan pretreated group when compared with control group (Tab.1, Fig.1, 2).

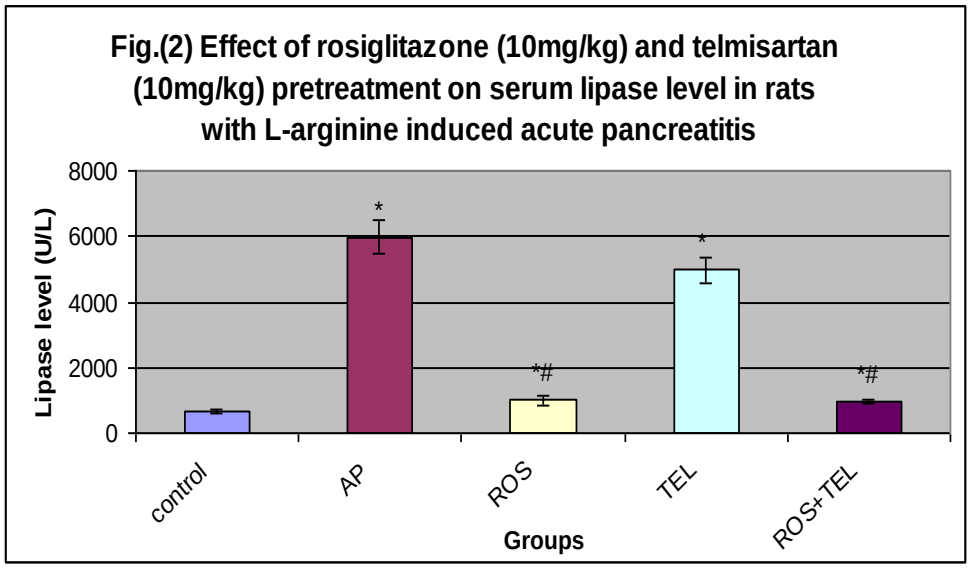
Pretreatment with rosiglitazone plus telmisartan produced marked improvement of acute pancreatitis manifested by the significant decreases ($P<0.05$) in serum levels of amylase and lipase compared with acute pancreatitis. While, there was a significant increase ($P<0.05$) in serum amylase and lipase when compared with control group (Tab.1, Fig.1, 2).

Table (1): Mean (±SE) Serum amylase (U/L), Serum lipase (U/L) reported in all studied groups (n=10)

Parameters Groups	Serum amylase (U/L)	Serum lipase (U/L)
Control	18.36±0.79	663±73
AP	863±15.8*	5965±513*
Ros	298±36.2*#	1003±147*#
Tel	795±18.2*	4978±394*
Ros+Tel	199±19.5*#	963±89*#

* : Significant difference versus control group.
\# : Significant difference versus AP.
AP : Acute pancreatitis
Ros : Acute pancreatitis treated with rosiglitazone (single dose 10mg/kg of bw by an orogastric catheter).
Tel : Acute pancreatitis treated with telmisartan (single dose 10mg/kg of bw by an orogastric catheter).





At 24hours after induction of AP, estimation of TNF-α and IL-6 serum levels show that L-arginine administration resulted in significant increase ($P<0.05$) in both parameters compared to control group (tab.2,Fig.3,4).

Pretreatment with rosiglitazone at the dose of 10mg/kg at the same time of induction of AP, produced marked improvement TNF-α and IL-6 serum levels ($P<0.05$) compared with AP group. While, there was a significant increase ($P<0.05$) in serum TNF-α and IL-6 in rosiglitazone pretreated group when compared with control group (tab.2, Fig.3, 4).

At the same time, Pretreatment with telmisartan at the dose of 10mg/kg of bw produced insignificant decrease ($P>0.05$) in improvement TNF-α and IL-6 serum levels ($P>0.05$) as compared to AP group. Also, there was a insignificant increase ($P>0.05$) in TNF-α and IL-6 serum levels in telmisartan pretreated group when compared with control group (tab.2, Fig.3, 4)

Furthermore, Pretreatment with rosiglitazone plus telmisartan, produced marked improvement TNF-α and IL-6 serum levels ($P<0.05$) compared with AP group. While, there was a significant increase ($P<0.05$) in serum TNF-α and IL-6 compared with control group (tab.2, Fig.3, 4).

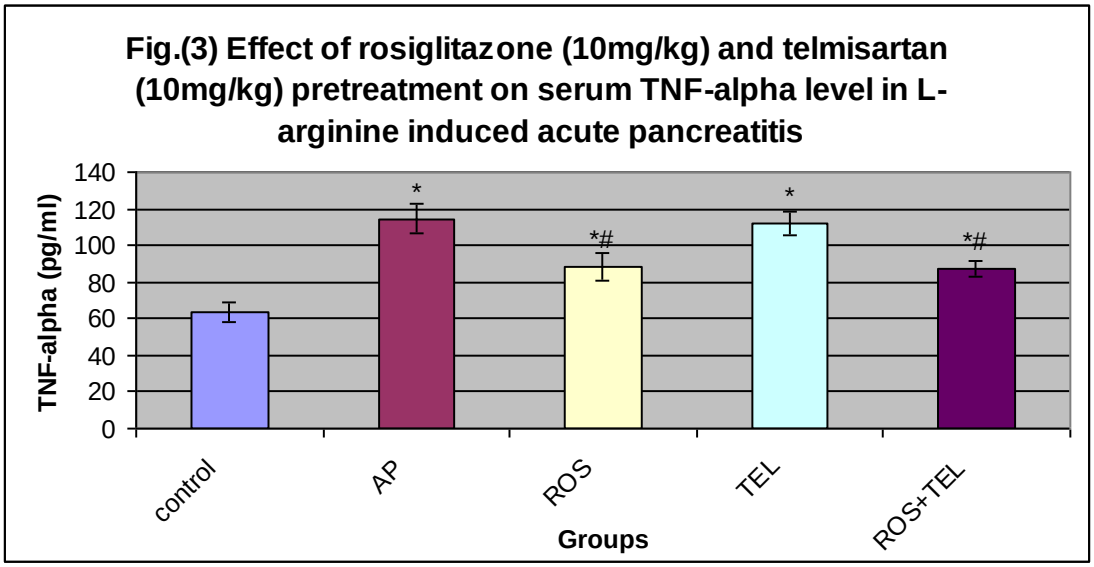
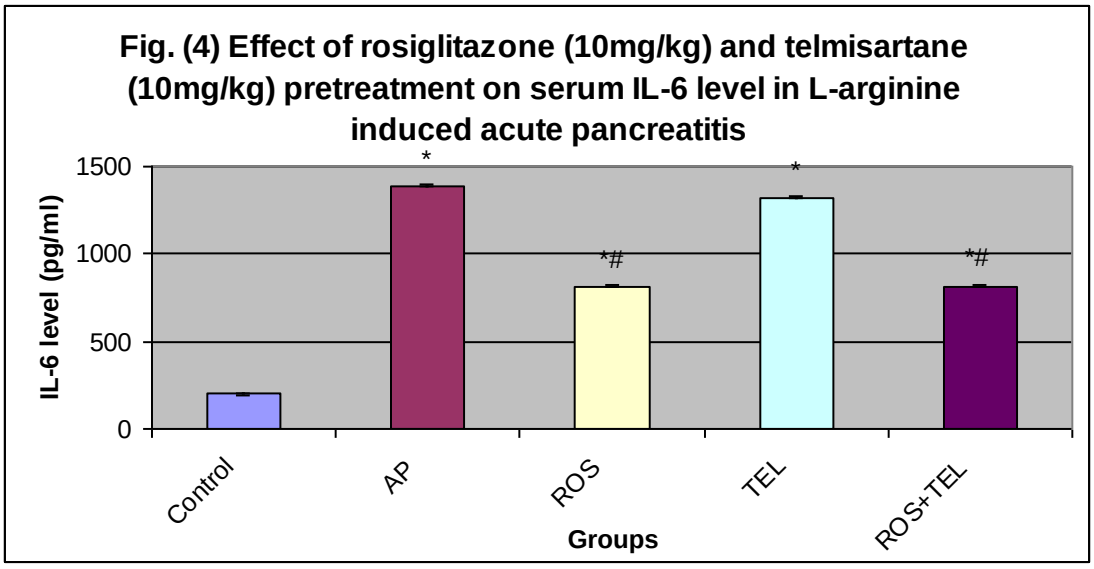


Table (2): Mean (±SE) TNF-α (pg/ml), IL-6 (pg/ml) reported in all studied groups (n=10)

Parameters Groups	TNF-α (pg/ml)	IL-6 (pg/ml)
Control	63.4±5.1	201.9±17.2
AP	114.4±7.9*	1391.8±106.6*
Ros	88.5±7.7*#	816.2±73.1*#
Tel	112±6.1*	1322.1±145*
Ros+Tel	87.7±4.3*#	814.9±80.3*#

* : Significant difference versus control group.
\# : Significant difference versus AP.
AP : Acute pancreatitis
Ros : Acute pancreatitis treated with rosiglitazone (single dose 10mg/kg of bw by an orogastric catheter).
Tel : Acute pancreatitis treated with telmisartan (single dose 10mg/kg of bw by an orogastric catheter).



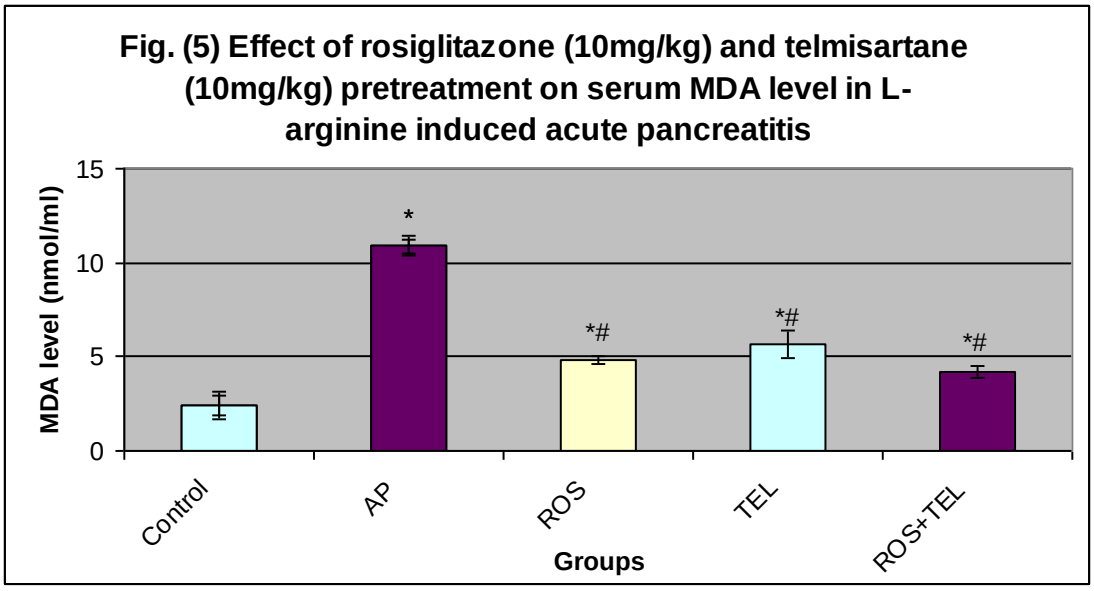
As regards malondialdhehyde (MDA) and catalase (CAT) activity, estimation of MDA and CAT serum levels show that L-arginine administration resulted in significance increase (P<0.05) in both parameters compared to control group (table 3, Fig.5,6).
Pretreatment with rosiglitazone at the dose of 10mg/kg at the same time of induction of AP, produced marked improvement MDA and CAT (P<0.05) compared with AP group. While, there was a significant increase (P<0.05) in serum MDA and CAT in rosiglitazone pretreated group when compared with control group (Table 3, Fig.5, 6).
At the same time, Pretreatment with telmisartan at the dose of 10mg/kg of bw produced significant decrease (P>0.05) in improvement MDA and CAT serum levels
(P<0.05) compared to AP group. Also, there was a significant increase (P<0.05) in MDA and CAT in telmisartan pretreated group when compared with control group Table 3, Fig.5, 6).

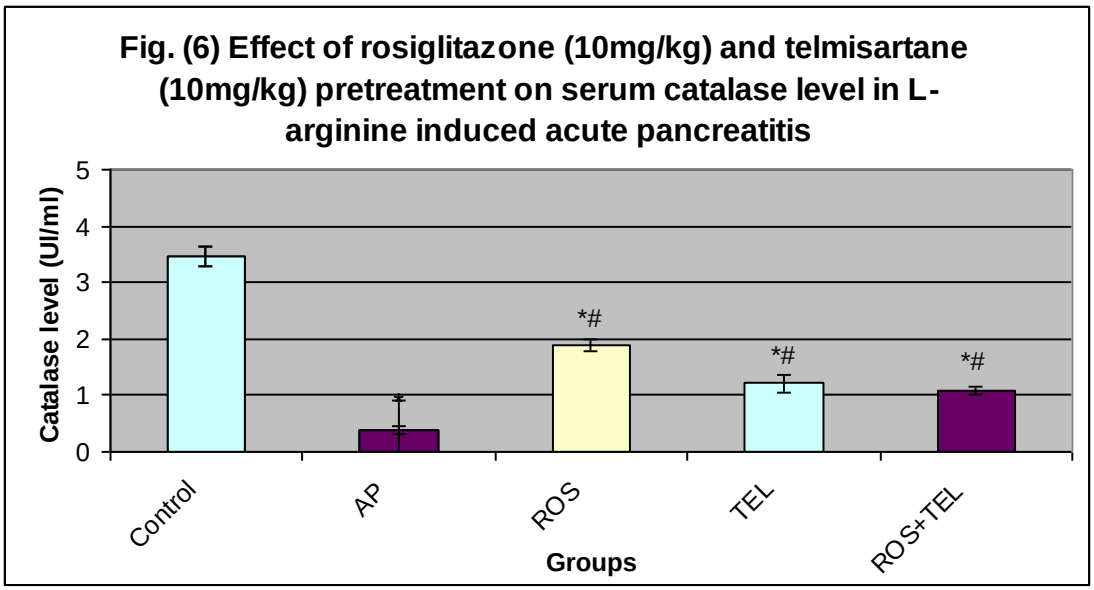
Table (3): Mean (±SE) MDA (nmol/ml) and CAT (U/ml) reported in all studied groups (n=10).

Parameters Groups	MDA (nmol/ml)	Catalase (U/ml)
Control	2.42±0.29	3.46±0.16
AP	10.87±0.52*	0.38±0.06*
ROS	4.85±0.22*#	1.89±0.07*#
TEL	5.65±0.71*#	1.21±0.11*#
ROS+TEL	4.21±0.35*#	1.09±0.09*#

* : Significant difference versus control group.
\# : Significant difference versus AP.
AP : Acute pancreatitis
Ros : Acute pancreatitis treated with rosiglitazone (single dose 10mg/kg of bw by an orogastric catheter).
Tel : Acute pancreatitis treated with telmisartan (single dose 10mg/kg of bw by an orogastric catheter).

While Pretreatment with rosiglitazone plus telmisartan produced marked improvement MDA and CAT (P<0.05) compared with AP group. While, there was a significant increase (P<0.05) in serum MDA and CAT compared with control group (Table 3, Fig.5, 6).





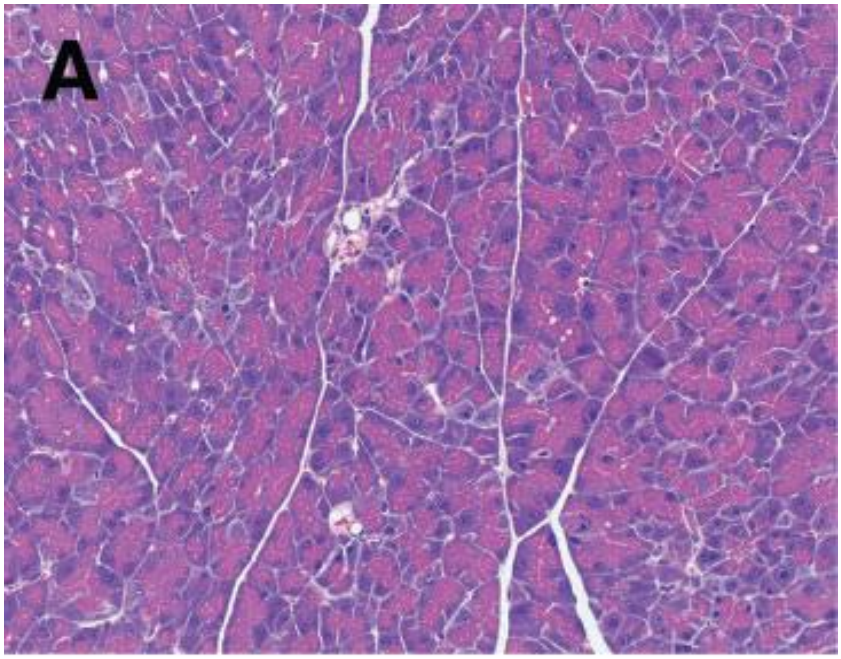
At the same time, the histopathological findings also supported these biochemical observations and indicated the presence of a severe form of AP in the pancreas of L- arginine-injected rats Fig.1B); which typically characterized by a high score of necrosis, vacuolization and edema of pancreatic acini, and inflammatory cell infiltration into the necrotic areas as compared with normal control group (Tab.1 Fig.1A).

Table (4):Histopathologic grading" of morphologic alterations of pancreatic gland in groups of rats .

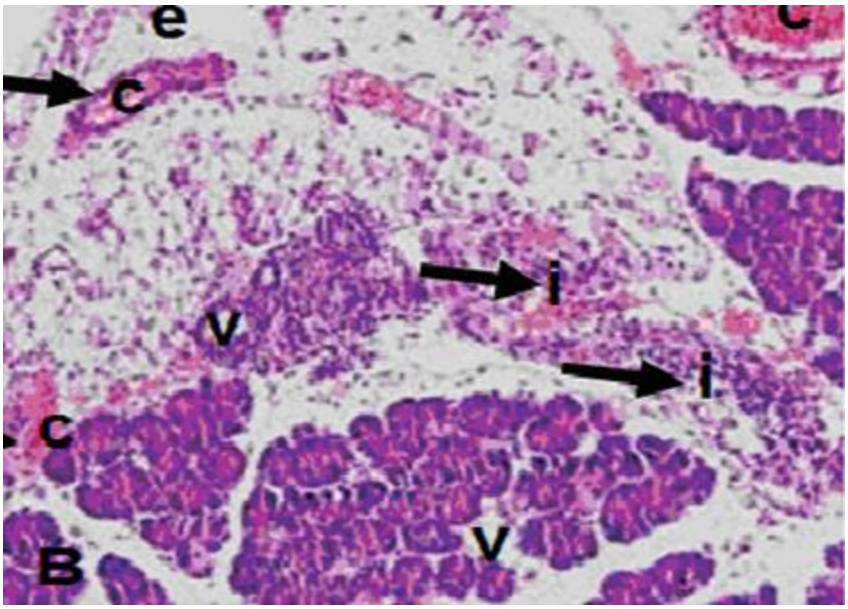
Parameters Groups	Edema	Vacuolization	Infiltration	Necrosis	Total
Control	0.00	0.00	0.00	0.00	0.00
AP	2.33±0.47*	2.75±0.60*	2.50±0.5*	0.42±0.64*	8.00±1.08*
Ros	1.58±0.04*#	1.62±0.62*#	1.92±0.00*#	00.00#	5.12±0.92*#
Tel	2.00±0.41*	2.25±0.72*	2.01±0.64*	0.17±0.37*	6.43±1.47*
Ros+Tel	1.54±0.50	1.59±0.42	1.85±0.00	00.00	4.98±0.41*#

* : Significant difference versus control group.
\# : Significant difference versus AP.
AP : Acute pancreatitis
Ros : Acute pancreatitis treated with rosiglitazone (single dose 10mg/kg of bw by an orogastric catheter).
Tel : Acute pancreatitis treated with telmisartan (single dose 10mg/kg of bw by an orogastric catheter).

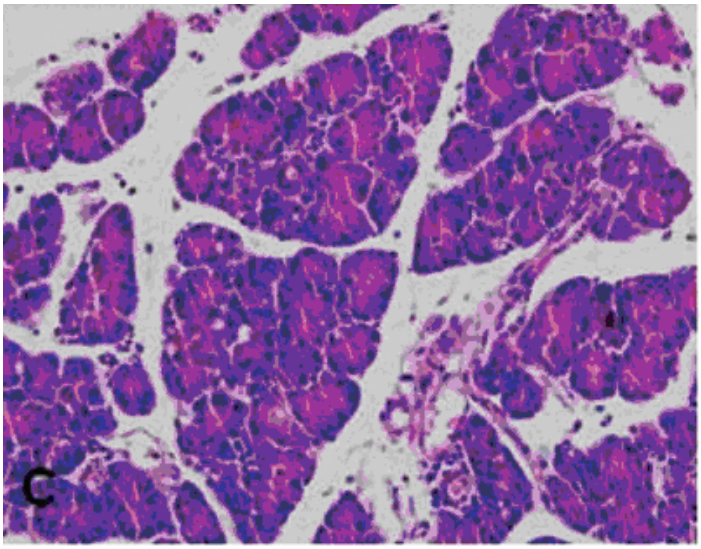
Fig.(7) Photomicrograph of pancreatic sections stained with hematoxylin- eosin



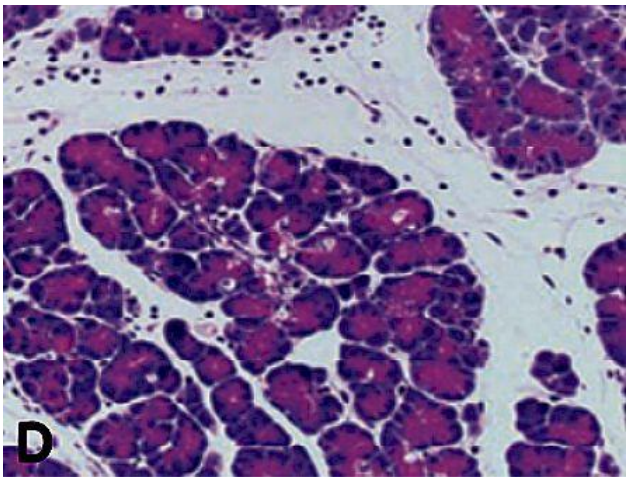
A section taken from the control rat shows normal pancreatic architecture, acini, blood vessels and normal islets of langerhans.



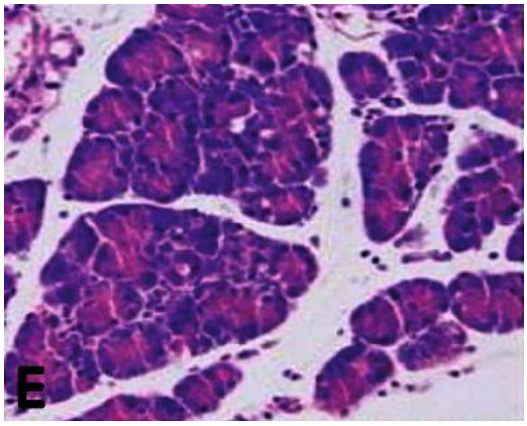
A section taken from the L-arginine induced acute pancreatitis shows sever interstitial edama "e",congested dilated vessels "c", vacuolization of acinar cytoplasm"v", and cellular inflammatory infiltration"i".



A section taken from rosiglitazone treated rats (10 mg/kg) shows a remarkable decrease in edema, disappearance of vacuolization and preservation of seminormal pancreatic acini.



A section taken from telmisartan treated rats (10 mg/kg) shows edema, less congestive blood vessels and vacuolization with cellular inflammatory infiltration. (magnificationX400).



A section taken from rosiglitazone+ telmisartan treated rats (10 mg/kg) shows a remarkable decrease in edema, disappearance of vacuolization and preservation of seminormal pancreatic acini and cellular inflammatory infiltration.

DISSCUTION

Experimental models of acute pancreatitis resembling the human situation are an integral tool for increasing the understanding of complex mechanisms as well as for developing therapeutic strategies for this disease

The present study aimed to explore the anti-inflammatory effects of the angiotensin type 1 receptor blocker telmisartan and rosiglitazone and their effect on peroxisome proliferator-activated receptor-γ (PPARγ)–activating properties by analysis of serum interleukin 6 levels and TNF-α in addition to histopathological manifestation in L-arginine induced acute pancreatitis in rats.

In this work, intraperitoneal injection of L-arginine was used to induce acute pancreatitis as this model produces non-surgical, selective and dose-dependent acinar cell necrosis [24]. Furthermore, it was proven that oxygen-derived free radicals play a role in pathogenesis of L-arginine induced pancreatitis [34].

L-arginine was chosen in this experiment and animals were sacrificed 24hours after the second L-arginine injection as by the time acute pancreatitis would be established as proven by previous experimental works [35,36,37]. This experimentally induced AP is manifested both biochemical and histological changes which are very similar to the human disease.

In the present study, induction of pancreatitis significantly increased serum amylase, lipase levels at 24h. Serum amylase and lipase levels have been traditionally utilized and the important diagnostic markers for acute pancreatitis. These observations are in consistence with previous results which revealed that serum amylase and lipase usually rise within 4-8 hours of the initial attack, peaks at 24 hours and returns to control level over the27hrs [38,39,40].The utility of serum amylase marker is complicated by significant limitations, including low sensitivity and specificity [41].Because the pancreas is the only source of lipase, plasma lipase estimations are specific for pancreatic injury [42].Serum lipase is recommended to replace or supplement amylase levels for the diagnosis of acute pancreatitis, an elevated lipase is virtually diagnostic for pancreatitis, approaching 100% specificity[43] .

In the present work, beside elevation of enzymes, plasma levels of pro-inflammatory cytokines (IL-6 and TNF-α) were significantly increased. Furthermore, serum level of MDA was remarkable increase with significantly decreased in serum catalase enzyme after induction of pancreatitis.

It is well known that the extent of pancreatic tissue damage in acute pancreatitis correlates with the levels of inflammatory mediators (IL, TNF and CRP) and free radical [35,38,44].Similarly, the current study confirms and extends previous findings [37] that demonstrated the L-arginine induced pancreatitis is accompanied by remarkable increased plasma levels of IL-6 and TNF-α, together with amylase after induction of AP. [[45,46] found that the increased serum TNF-α, IL-6 andIL-1 levels were demonstrated at 24hs after the induction of pancreatitis with L-arginine in rat. Moreover [47,48] reported that increase serum level of TNF-α and IL-6 were detected 12hrs after adminstration of L-arginine and remained elevated at 48hrs versus normal control.

In consistent with our reports, [49] demonstrated that the pancreatic MDA level was significantly elevated at 24hrs and peaked at 48hrs after adminstration of L-arginine. In addition, the endogenous scavengers, superoxide dismutase and catalase activities decreased significantly throughout the entire study versus control. In accordance with this work, the results of [50] indicate that Oxygen free radicals (OFR) play an important mediator function in early and later courses of AP. Their findings suggest that OFR species are important mediators but not necessarily triggers of tissue damage in AP. Also, [37,38]) stated that induction of pancreatitis significantly increased the pancreatic total protein, MDA, nitrite, catalase and SOD and decreased the GSH levels. Lipid peroxidation is a process mediated by free radicals, which results in impairment of the membrane functional and structural integrity.

In addition, acute pancreatitis was also confirmed in our study by typical inflammatory features observed microscopically during the same duration in the present study, histopathological assessments revealed that induction of pancreatitis resulted in pancreatic damage characterized by acinar cell necrosis, cell infiltration, edema and haemorrhage this in agreement with previous reports by [34,38] .

The present study focuses on the effect of rosiglitazone and telmisartan on experimental acute pancreatitis and possible anti-inflammatory and antioxidant effects. Rosiglitazone alone and in combination with telmisartan efficiently reduced serum amylase and lipase levels. The anti-inflammatory response in the pancreas reflected in reduced serum levels of TNF-α and IL-6. In this work, we have also evaluated the anti-oxidant effect of both drugs in experimental acute pancreatitis, our data indicate that they exhibit an antioxidant effect as evidenced by significant decrease in serum MDA with increase in catalase enzyme activity, this confirmed by histopathological manifestation improvement compared to acute pancreatitis

These results are in agreement with [51] who found statistically significantly decreased activity of amylase, lipase and pancreatic inflammation in male mice treated with rosiglitazone in course of edematous cerulean-induced acute pancreatitis. A study of[52] revealed that rosiglitazone acts directly through PPAR-γ in acini, duct and islets to suppress markers of the inflammatory response developed during cerulean-induced acute pancreatitis as the cell type specific knockout of PPAR-γ in epithelial cells of pancreas removes the inflammatory cytokine production, pancreatic edema and infiltration.

Several studies have demonstrated that the use of PPAR-γ ligands inhibits the intensity of the inflammatory response in different processes including colitis [53], adjuant-induced arthritis [54] and cerulien induced pancreatitis [51]. There are more and more reports suggesting that PPAR plays a crucial role in the development of immune reaction; particularly in inflammation [55,56]. PPARs-γ present in the alimentary canal (the liver, pancreas, large intestine) are characterized by the widest spectrum of the effects mentioned [57,58]. The receptors might be indirectly activated by synthetic ligands such as thiazolidinediones (troglitazone, ciglitazone, pioglitazone, rosiglitazone [59]. Many studies describe beneficial effects of PPAR-γ stimulation on inhibition of gastro-intestinal inflammation. The literature available, including studies in animal models, demonstrates decreased expression of inflammatory

cytokines, such as TNF-a, IL-1b, IL-6 and myeloperoxi- nki [60.61].According to some other experimental studies, PPAR-γ ligands, through selective blockage of NF-kB signaling pathway in vitro, lead to a significant decrease in inflammatory IL-8 and MCP1 expression [62,63].

A cross-talk between pro-inflammatory cytokines and oxidative stress occurs in the development of the inflammatory response in AP, particularly TNF-alpha amplifies the inflammatory cascade through different mechanisms , such as the activation of mitogen activated protein kinases and nuclear factor-kappa B (NF-kB) and/or the inactivation of protein phosphatases[64,65]. The current study confirms and extends previous reports, for example PPAR-γ stimulation by rosiglitazone reserved the oxidative changes induced by cold restraint stress (CRS). Rosiglitazone protective treatment significantly reduced gastric mucosal MDA and SOD activity and increase CAT activity, restoring their normal balance. [66.67]. The ROS lowering effect of the PPAR-γ agonist, rosiglitazone could be attributed to its inhibitory effect on TNF-α, an inflammatory mediator that increases ROS production during CRS. Furthermore, it has been reported that rosiglitazone has antioxidant activity and improves enzymatic antioxidant parameters like superoxide dismutase, catalase and glutathione peroxidase [67,68]which was confirmed in the present study.

Our results demonstrated that telmisartan was unable to alter the increased serum amylase and lipase levels to significant level. Also, inflammatory response showed insignificant reduced serum levels of TNF-α and IL-6 in telmisartan treated than experimental acute pancreatitis. In addition, we have evaluated the anti-oxidant effect of telmisartan which demonstrated significant improvement versus experimental acute pancreatitis. Combination of rosiglitazone and telmisartan treated rats was insignificantly improved parameters of AP compared to rosiglitazone alone but significant compared to AP.In accordance with previous reports, [69] reported that lesser serum TNF-α concentration in rosiglitazone and combination treatment as compared to disease control rats while rats treated with telmisartan showed higher serum concentration as compared to rats treated with rosiglitazone or its combination with telmisartan. These data suggest that telmisartan alone is ineffective in controlling TNF-α release. Effect observed in combination group is only due to the rosiglitazone which inhibits the TNF-α and attenuates the disease. Also, [70] reported that, in low-risk patient population, telmisartan (80 and 160 mg) treatment did not significantly affect serum interleukin 6 levels. These data are in contrast to a previously published study by [71]. In this study, the ARB olmesartan exhibited potent anti-inflammatory actions by reducing C-reactive protein, tumor necrosis factor-α, IL-6, and monocyte chemoattractant protein 1 serum levels .Also, [72,73] reported that telmisartan manifests powerful anti-inflammatory effects beyond class effects of angiotensin II Type 1 blocker by inhibiting TNF-α, induced IL-6 expressions through Peroxisome Proliferator Activated Receptor γ Activation .

[74] Observed that Telmisartan directly ameliorates IL-1β-induced neuronal inflammatory response by inhibition of oxidative stress and the JNK/c-Jun pathway. This observation supported our result that the insignificant decrease in pancreatic inflammation of telmisartan may be due to antioxidant effect.

The histopathological manifestations in this work confirmed other results. These results supported by [69] who used rosiglitazone and telmisartan alone or in combination as anti-inflammatory in rheumatoid arthritis, through their observation that histopathology of synovial joint showed decreased vascular proliferation, decreased cartilage destruction, lesser decrease in synovial joint space and decreased chondrocytes migration in rats treated with rosiglitazone as compared to disease controlled rats. Rats treated with telmisartan showed higher cartilage destruction, higher vascular proliferation, decreased synovial joint space and higher chondrocytes migration as compared to rats treated with rosiglitazone or its combination with telmisartan. These findings suggest that telmisartan alone is ineffective in controlling the progression of Rheumatoid arthritis as compared to rosiglitazone. In contradicting to our results, [75] demonstrated that blockade of AT1 receptor by an AT1 receptor antagonist may act by normalizing pancreatic blood flow, resulting in reduced pancreatic inflammation.

From the previous observation we suggest that rosiglitazone is a potent anti-inflammatory in AP. On the other hand telmisartan was unable to reduce inflammation in AP in spite of telmisartan's bimodal mechanism of action (AT_1 receptor blockade + PPARγ modulation). These observations can explain by other investigators, who revealed that TZDs agents were shown to act by stimulating a member of the nuclear hormone receptor family, Peroxisome proliferator–activated receptor (PPAR). TZDs are agonists for PPAR-γ, and, when bound to PPAR-γ receptor, lead to modulation of expression of specific genes, thus inhibiting production of a number of inflammation mediators when used at higher doses and hence it is having more adverse effect like weight gain and fluid retention [76]. There is also a newer class of this family called Selective PPAR-γ Receptor Modulators (SPPARMs). These are the agents that partially activate the receptor by binding at the different site than the full agonist binds hence also called as partial agonist. Telmisartan, an antagonist of Angiotensin 2 type 1 is a SPPARM. In addition to its AT_1 receptor–blocking properties [77,78,79]Compared with glitazones, as full PPARγ agonist, telmisartan binds to the receptor in a different manner, resulting in distinct pharmacological actions. The lesser efficacy of telmisartan (binds to the receptor in a different manner) compared to rosiglitazone could be due to its partial agonistic activity on PPAR-γ [69].

The discrepancy between our results and other data may relate to the doses used.
These results are supported by the finding of several previous studies that indicated a dose dependency of telmisartan-mediated PPARγ activation and show that further induction of monocytic PPARγ can be achieved with higher doses [70].

Several studies have shown that the RAS is present intrinsically in the pancreas and that its level is enhanced during acute pancreatitis and chronic pancreatic hypoxia in experimental animals [80,81,82],suggesting the role of the RAS in pancreatic diseases. However, there are several controversial reports regarding the effects of the inhibition of the RAS on acute pancreatitis. For example, [83] reported that losartan, an AT1 receptor antagonist, ameliorates cerulean induced acute pancreatitis in rats. Moreover, [84] reported that ramipril, an angiotensin-converting enzyme (ACE) inhibitor, enhances acute pancreatitis in the same model.
In addition [85] demonstrated that the ANG II-AT1 receptor pathway is not essential for the local pancreatic injury in acute pancreatitis but plays an important role in the development of pancreatic fibrosis through pancreatic stellate cell (PSC) activation and proliferation.

[86,87] reached far more that, they reported that clinicians should be aware to some ARB as irbesartan or losartan may cause acute pancreatitis. If abdominal pain develops, the medication should be discontinued and the patient investigated for acute pancreatitis. Angiotensin II receptors are thought to be important in regulation of pancreatic secretion and microcirculation, but the mechanism of pancreatitis induced by angiotensin II receptor antagonists remains unclear.

CONCLUSION:

Hence on the basis of the above discussion, our study adds some support to previous experimental findings, use of rosiglitazone associated with a reduced risk of AP by improving inflammatory status and oxidative stress reflecting the important role of PPAR-γ in AP. Furthermore, telmisartan does not ameliorate acute pancreatic inflammation. Both agents have affinity for PPAR-γ, telmisartan binds to the receptor in a different manner, resulting in distinct pharmacological actions. Further studies are needed to establish the full potential effect of high-dose telmisartan therapy.

ACKNOWLEDGEMENTS

The authors would like to thank Faculty of Medicine, Benha University especially Dr Asmaa M. Elhady lecturer of histopathologylogy for her sincere help and her effort in this work.

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