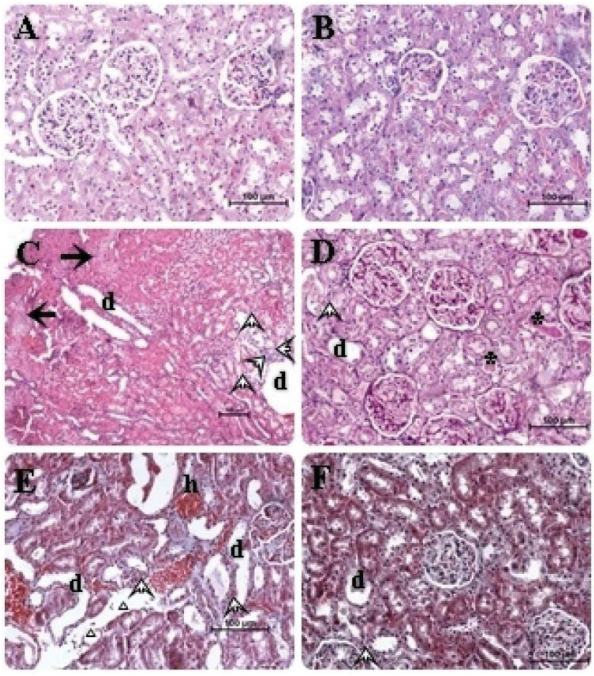

Figure 1. Photomicrographs of hematoxylin and eosin stained sections of kidney of rats (kidney histology magnification 200×). Typical features of normal histological appearence of the corticomedullary region of rat kidney sections are observed in control and EP administered groups (A, B). In kidney sections of cisplatin pretreated rats, marked changes were observed in tubulus and glomerule structures. In some corticomedullary regions focal tubular necrosis (big solid arrows), haemorrhagia (small letter h) and dilatation (small letter d) as well as inflammatory cell infiltration (small hollow triangle) in the intersititium can be seen. Furthermore, necrotic cell debris and vacuolization (arrow heads) in tubulus epithelium and protein casts in tubular lumina are evident (C, E). The sections obtained from the cisplatin + EP group are found almost similar to that of those in the control group. Rare inflammatory cell infiltration, minimal (asteriks symbols) tubular dilatation and vacuolization images can be seen. It is considered that the renal injury induced by cisplatin is prevented to a great extent by EP co-administration (D, F).

Table 2. In addition to inflammatory cell infiltration, we also observed widespread tubular necrosis and dilatation of the proximal tubules especially in the S_3 segment and protein casts, necrotic cell debris in the tubular lumina of cisplatin group versus control group which are in agreement with previous studies (Figure 1(C) and 1(E)).[7,35]

Lipid peroxidation and inflammation are closely related with each other. Thus, in a rat model of hepatic ischemia/reperfusion injury, Tsung et al. [16] have recently reported that EP decreases hepatic lipid peroxidation and apoptosis partially by reducing neutrophil accumulation and lowering the level of inflammatory cytokines. In other studies, it has been shown that EP can inhibit the activation of pro-inflammatory signaling pathways like NF-$_K$B,[32,36] and down-regulates the release of multiple pro-inflammatory proteins, such as IL-6 and TNF-α.[37] More recently, Yousef et al. [38] indicated that hydroxy radicals have a potential of activating mitogen-activated protein kinase which plays a critical role in cisplatin-induced acute renal damage and inflammation, through the generation of TNF-α. In an experimental model of cardioplegia, it has been shown that pyruvate has also a potential of scavenging hydroxyl radical.[11] Thus, Wang et al. [29] demonstrated that certain ROS scavengers are also anti-inflammatory agents. In this study, the severity of the tubular damage was significantly decreased in the EP co-administered group (Figure 1(D) and 1(F)) (Table 2). Less tubular dilatation and necrosis and inflammatory cell infiltration were also observed in the same EP + cisplatin group (Figure 1(D) and 1(F)) (Table 2). These data indicate that a significant compensation was constituted by EP against cisplatin nephrotoxicity. This compensation seems to be likely related with the potent antiimflammatory and antioxidant activity of EP.

The major ROS generated in the organism are superoxide anions and their derivatives particularly highly reactive hydroxyl radical attack nucleic acids, proteins, lipids and induce oxidation of these biomolecules which trigger lipid peroxidation.[21] Alterations in membrane structure and functions by lipid peroxidation induce cellular damage and are responsible for ROS-induced organ failure. Thiobarbituric acid substances (TBARS) are produced by lipid peroxidation and are considered as indicators of oxidative stress.[39]

MDA levels of the groups in this study are shown in Table 1. Renal tissue MDA (which is an end product of

Table 2. Histopathological findings in the different study groups.

	Control	EP	CIS	CIS + EP	p^*
Tubular necrosis	0	0	3	1	$p < 0.01^*$
Tubular dilatation and haemorrhagia	0	0	3	1	$p < 0.01^*$
Necrotic cell debris, vacuolization	0	0	2	1	$p < 0.05^*$
Protein casts	0	0	2	1	$p < 0.05^*$
Inflammatory cell infiltration	0	0	2	1	$p < 0.05^*$

Note: 0: no observed changes; 1: mild changes; 2: moderate changes; 3: severe changes. EP: ethyl pyruvate only treated group; CIS: cisplatin only treated group; CIS+EP: cisplatin+ethyl pyruvate treated group.
*CIS group was compared with the other groups.