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AMELIORATIVE EFFECT OF FRESH GARLIC AND VITAMIN E AGAINST LINEZOLID INDUCED HEPATO-RENAL OXIDATIVE DAMAGE IN RATS

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ABSTRACT

The present study was conducted to compare between the protective effect of either garlic or vitamin E (Vit E) against hepatic and renal damage induced by 100mg/ kg linezolid (LNZ) administration. Thirty male albino rats were allocated into equal six groups; first three control groups; (control, tween 80 and olive oil); Group4; received 100mg LNZ / kg for 14 consecutive days. The last two groups were administered either garlic (500 mg/kg) or Vit E (100 mg/kg) prior to LNZ administration daily for 14 consecutive days. Blood samples were obtained from all rats for biochemical investigations and oxidative stress biomarkers. Specimens from liver and kidneys were excised for histopathological investigation. Linezolid induced a significant elevation in serum Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP) and urea. Alterations in antioxidant / oxidant status were noticed during LNZ administration**.** Administration of garlic or Vit E modulated the previous parameters and restored histological structures. In conclusion, both garlic and Vit E were able to ameliorate hepato-renal alterations induced by LNZ via their antioxidant effects.

Key words: Linezolid, Garlic, Vitamin E, Kidney Liver.

INTRODUCTION

Recently, the broad activity of linezolid (LNZ) against gram- positive pathogens enables it to be a commonly prescribed antibiotic in clinics. Little studies were conducted to manage toxicities related to LNZ. Linezolid is an oxazolidinone antibiotic, it acts broadly against gram-positive micro-organisms via inhibition bacterial protein synthesis. It contorts the tRNA binding site overlapping the two ribosomal subunits 50S and 30S and inhibits protein synthesis before it starts (Tripati, 2014).

Linezolid oral bioavailability is a round 100%, permitting a move from the intravenous administration to the oral route without dose adjustment (Hombal *et al.,* 2017). Hepatotoxicity (Vivekanandan *et al.,* 2018), renal dysfunction (Takahashi *et al.,* 2011), optic neuropathy, lactic acidosis (Carbajo *et al.,* 2011) and bone marrow suppression (Bishop *et al.,* 2006) are LNZ- associated adverse effects. Vinh and Rubinstein, (2009) demonstrated that LNZ use is associated with disturbances in liver enzymes. Linezolid treated rats showed a significant elevation in lipid peroxidation markers such as MDA in the liver and cause free radical-induced liver damage (Vivekanandan *et al.,* 2018). LZD represses cell proliferation and delays the cellular metabolic activity by influencing the mitochondrial function (Duewelhenke *et al.,* 2007).

Natural origin, weak side effects and cost effectiveness expand the use of natural supplements and medicinal plants in treatment or even using them to alleviate the adverse action of certain drugs. There are little studies which used natural antioxidants to alleviate LNZ detrimental effects. Garlic *(Allium sativum*), a member of the Liliaceae family, is one of the most popular herbs used in modern folkloric medicine (Chinnala *et al.,* 2018). Garlic is commonly used as immunomodulatory, hepatoprotective, (Uma *et al.,* 2007), and antioxidant agent (Schäfer and Kaschula, 2014). Garlic has two main classes of antioxidant machineries, flavonoids and sulfur-containing compounds (diallyl sulfide, trisulfide and allyl-cysteine (Shirzad *et al.,* 2011). Vitamin E (Vit E), a strong lipid-soluble antioxidant, counteracts reactive oxygen species (ROS) damage in polyunsaturated fatty acids and acts against damage caused to phospholipids as a membrane-stabilizing

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agent (Bradford *et al.,* 2003).Vitamin E can prevent liver damage, fibrosis and cirrhosis progression during exposure to toxic substances (Sokol, 1996). The present work was conducted to study the ameliorative effect of garlic and Vit E on biochemical and histopathological disturbances associated with LNZ treatment in male albino rats in a trial to improve LNZ clinical use.

MATERIALS AND METHODS

Reagents and drugs

Linezolid (LNZ) tablets (600 mg) obtained from Global Napi Pharmaceuticals Company, Egypt. Vitamin E (Vit E) capsules (1000 mg) purchased from Pharco Pharmaceuticals Company, Egypt.

Fresh garlic was obtained from local market and cleaned, washed. The cloves were peeled, weighed, added to suitable cold distilled water, grounded by mixer. The garlic homogenate was administered within 30 minutes of preparation**.**

Animals management and designing

Thirty apparently healthy adult male albino rats, weighing 200±10 g were obtained from the Laboratory Animal House, Faculty of Veterinary Medicine, Zagazig University, Egypt. The animals were housed in metal cages under optimal conditions. They were subjected to feed rodent diet *ad libitum* with free access to fresh water throughout the experimental period. Rats were acclimatized for 14 days before the experiment. The care and use of the animals confirmed to the rules of the institutional Animal Care and Use Committee of the Faculty of Veterinary Medicine, Zagazig University, Egypt.

After weighing the rats, they were randomly allocated into equal six groups (n= 5 each). The first three groups were kept as control groups, 1st group, rats was kept without any treatment. 2nd group (tween 80), rats were given the diluting vehicle of LNZ (tween 80) in form of 0.5 ml /200 g / day. 3rd group (olive oil), rats received the diluting vehicle of Vit E as 0.2 ml olive oil once daily. 4th group (LNZ), rats administered 100mg LNZ/ kg/day (Aytan *et al.*, 2009) dissolved in tween 80. 5th group (garlic+ LNZ), rats were given 500 mg fresh garlic /kg / day (Banerjee *et al.,* 2002) 1 h before LNZ dosing. 6th group (Vit E+ LNZ), rats received 100 mg Vit E /kg /day (El-Demerdash *et al.,* 2004) dissolved in olive oil 1 h before LNZ administration. All rats were administered their doses orally using oral gavage needle daily for 14 consecutive days.

Blood sampling

At 15th day after the end of experiment, all rats were euthanized. Blood sample was collected in plain tube without anticoagulant, and then centrifuged at 3000 rpm for 10 minutes for serum collection until screening of liver and kidney damage biomarkers.

Biochemical and oxidative status assessment

Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) were measured according to (Reitman and Frankel, 1957) and alkaline phosphatase (ALP) was estimated according to (Kind and King, 1954). Urea and creatinine were determined as previously described by (Fawcett and Scott, 1960) and (Henry *et al.,* 1974) respectively. All parameters were measured using commercial kits (Diamond Diagnostic Company, Spinreact). Serum catalase (CAT), superoxide dismutase (SOD) and malondialdehyde (MDA) levels were estimated using commercial ELISA kits (Cusabio Biotech. Co., Ltd.,) by the methods of (Aebi, 1984), (Nishikimi *et al.,* 1972) and (Ohkawa *et al.,* 1979) respectively.

Histopathological investigation

After euthanization, specimens of liver and kidneys were collected from 5 rats /each group, fixed in 10% neutral buffered formalin solution. After that, they were embedded in paraffin, then 5 µm sections were cut, stained with hematoxylin and eosin (H&E) and finally examined under microscope.

Statistical analysis

The obtained data was represented as mean ± SE. The values were analyzed by ANOVA followed by Duncan's test. The data were considered significant at $P \leq 0.05$ (Tamhana and Dunlop, 2000).

RESULTS

Effect of garlic or Vit E on biochemical and oxidative stress biomarkers in male albino rats treated with LNZ

Data in Table 1 represented a significant increase in serum AST, ALT, ALP in rats orally administered LNZ comparing with control groups. The rats given garlic or Vit E with LNZ had significantly reduced AST, ALT, ALP levels as compared with LNZ treated rats. Urea levels showed a significant increase in LNZ treated rats in comparison with control groups. Garlic and Vit E ameliorated the increase in urea levels compared to LNZ group (Table 2). Creatinine concentration revealed a non significant change in all treated groups.

Compared to control groups, lipid peroxidation was markedly increased in LNZ treated group as represented by a significant increase in MDA level. Treatment with either garlic or Vit E expressed a significant decrease in MDA level comparing to LNZ group. Moreover, CAT and SOD were significantly decreased in LNZ treated rats comparing to control rats. Both CAT and SOD were significantly elevated in groups administered either garlic or Vit E (Fig 1).

Table 1: Effect of garlic or Vit E on serum AST, ALT, ALP in male albino rats treated with LNZ.

Groups	Parameters		
	AST (U/L)	ALT (U/L)	ALP (U/L)
Control	19.66 ^{d} ± 0.88	13.68 ^{d} ± 1.20	72.10 ^{d} ± 1.37
Tween 80	17.5 ^{d} ± 3.5	14.00 ^{d} ± 3.00	71.30 ^{d} ± 0.40
Olive oil	19.00 ^{d} ± 1.73	13.00 ^{d} ± 1.53	71.87 ^{d} ± 1.47
LNZ	50.25 ^{a} ± 1.49	54.75 ^{a} ± 2.01	130.62 ^{a} ± 3.87
Garlic+LNZ	40.75 ^{b} ± 0.85	38.00 ^{b} ± 1.82	106.32 ^{b} ± 2.17
Vit E+LNZ	32.00 ^{c} ± 1.08	23.75 ^{c} ± 1.49	90.22 ^{c} ± 1.34

Values are expressed as mean±SE. The different superscripts (a-d) for the same parameter are significantly different at P≤ 0.05. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; LNZ: Linezolid; Vit E: Vitamin E. (n=5).

Table 2: Effect of garlic or Vit E on serum urea and creatinine in male albino rats treated with LNZ.

Groups		
	Urea (mg/dL)	Creatinine (mg/dL)
Control	27.46 ^{d} ± 0.99	0.79 ^{a} ± 0.03
Tween 80	27.30 ^{d} ± 1.40	0.76 ^{a} ± 0.02
Olive oil	27.33 ^{d} ± 0.49	0.79 ^{a} ± 0.02
LNZ	60.67 ^{a} ± 1.95	0.77 ^{a} ± 0.02
Garlic+LNZ	44.10 ^{b} ± 1.89	0.77 ^{a} ± 0.02
Vit E+LNZ	36.20 ^{c} ± 1.47	0.74 ^{a} ± 0.04

Values are expressed as mean±SE. The different superscripts (a-d) for the same parameter are significantly different at P≤ 0.05. LNZ: Linezolid; Vit E: Vitamin E. (n=5).

Figure 1

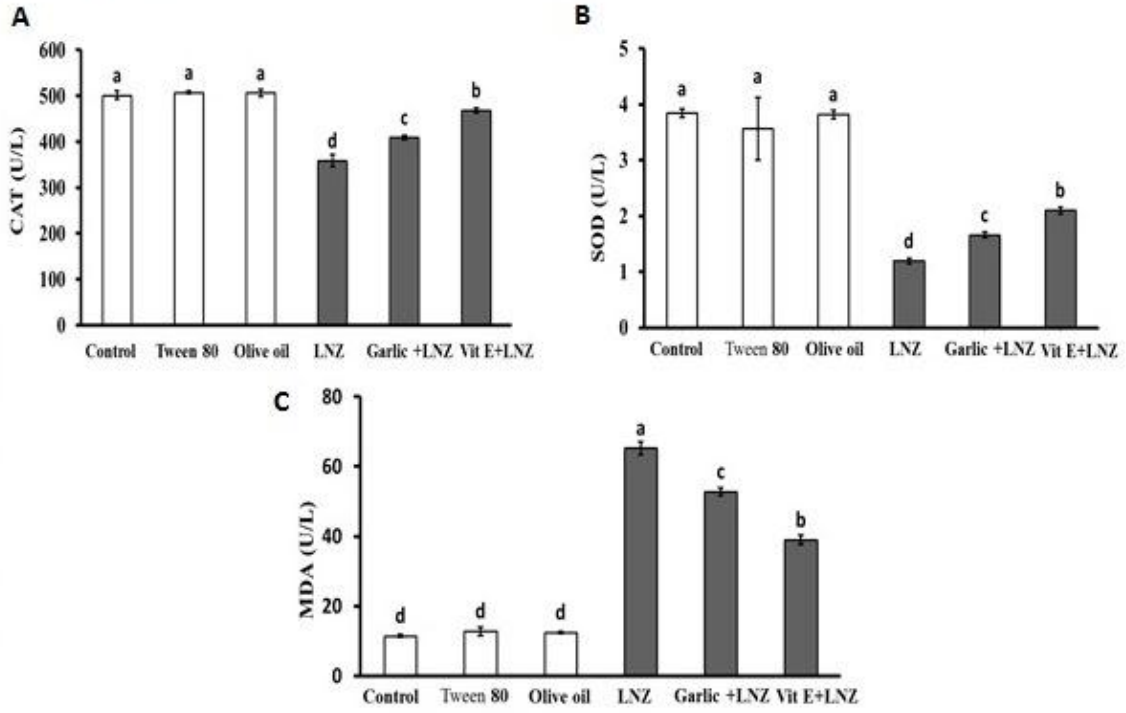

Figure 1: Effect of garlic and/or Vit E on antioxidant/oxidant status in male albino rats treated with LNZ. A: CAT (U/L). B: SOD (U/L). C: MDA (U/L). Values are expressed as mean±SE. Different letters above the bars indicant significant difference at P≤ 0.05. (n=5). CAT: Catalase; SOD: Superoxide dismutase; MDA: Malondialdehyde; LNZ: Linezolid; Vit E: Vitamin E.

Figure 2

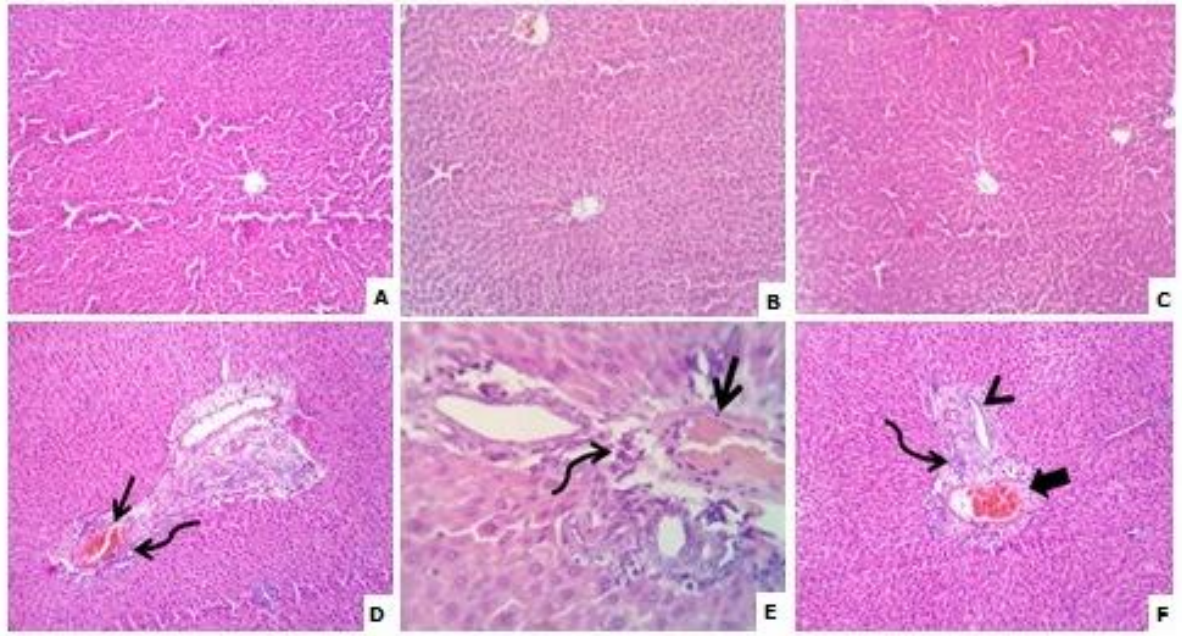

Figure 2: (A-F) Photomicrograph of hepatic H&E stained sections, normal histological structures in control, tween 80 and olive oil group (A), (B) and (C) (H&Ex100) respectively. Moderate congestion of hepatic portal blood vessels (open arrow) with moderate round cells infiltration (curved arrow) in LNZ group (D) (H&Ex100). Garlic +LNZ group showed mild portal biliary proliferation, congestion (open arrow) and a few round cells (curved arrow) (E) (H&Ex400). Mild congestion of hepatic blood vessels (thick arrow), round cells infiltration (curved arrow) and biliary proliferation (arrow head) in Vit E+ LNZ administered rats (F) (H&Ex100).

Figure 3

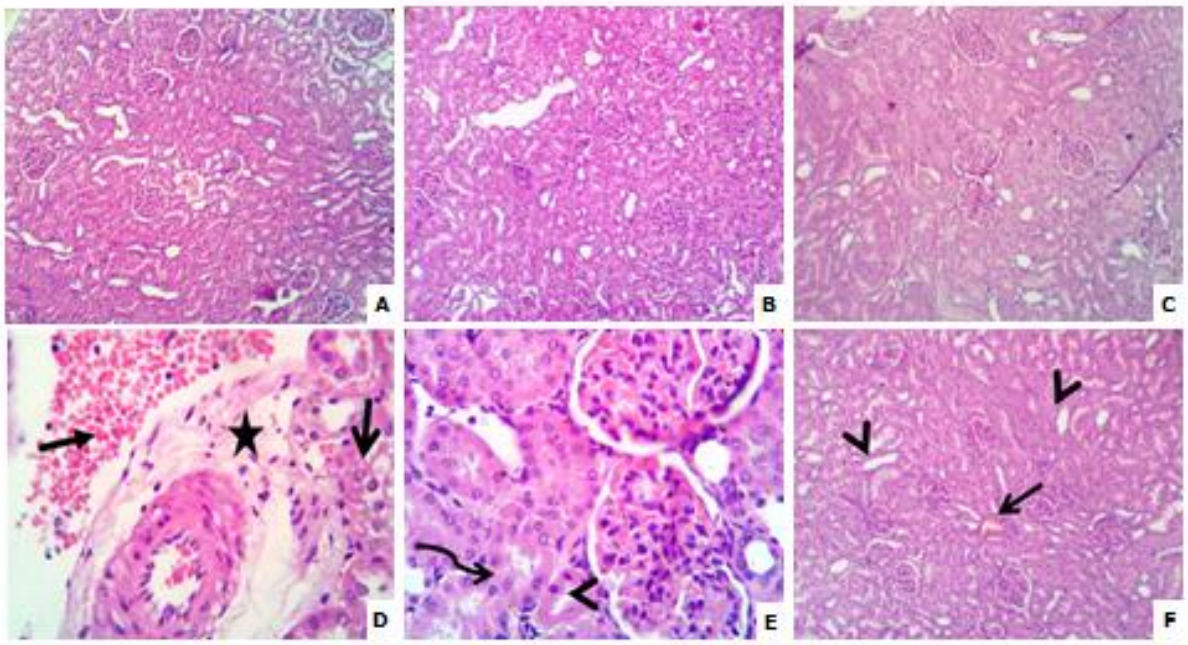

Figure 3: (A-F) Photomicrograph of renal tissue H&E stained sections, normal histological findings in control, tween 80 and olive oil treated rats (A), (B) and (C) (H&Ex100) respectively. LNZ administered rats showed perivascular edema (star), sometimes with hemorrhages (closed arrow).The renal tubular epithelium especially in the cortex showing degenerative changes (open arrow) (D) (H&Ex400).Mild dilatation of some proximal and distal convoluted tubules and degenerative (curved arrow) changes (arrow head) in garlic+ LNZ group (E) (H&Ex400). Mild congestion of some renal blood vessels (open arrow) and mild dilatation of some proximal and distal convoluted tubules (arrow heads) were observed in Vit E+LNZ treated rats (F) (H&Ex100).

Histopathological findings

Liver

Normal hepatic parenchyma with preserved lobular pattern, portal triads structures, vascular tree, kupffer cells and stromal component were observed in control groups (control, tween 80 and olive oil) (Fig. 2 A, b and c). Congestion of hepatic portal blood vessels and moderate round cells infiltration and biliary proliferation were seen in LNZ treated rats (Fig. 2D). Garlic+ LNZ treated group showed mild changes in portal area as mild portal biliary proliferation, congested portal blood vessels and few round cells infiltration (Fig. 2E). Meanwhile, normal structures with minimum residual tissue changes as mild congestion, round cells infiltration and biliary proliferation in the portal area of rats treated with Vit E prior to LNZ (Fig. 2F).

Kidneys

Light microscopical examination exhibited normal nephron units with preserved glomerular and tubular structures. The blood vessels and the stroma were within normal limits with normal histomorphology in the first control groups (control, tween 80 and olive oil) (Fig. 3 A, B and C) respectively. Linezolid treated rats showed modertae congestion of renal blood vessels with vacuolation of the vascular wall and perivascular edema, sometimes with hemorrhages, dilated collecting tubules. The renal tubular epithelium especially in the cortex showed degenerative changes mostly hydropic degeneration and necrotic changes (Fig. 3D). Mild dilatation of some proximal and distal convoluted tubules and mild degenerative changes in some renal tubular epithelium mostly cloudy swelling were seen in garlic+ LNZ treated group (Fig. 3E). Vit E+ LNZ group revealed preserved histomorphology of nephron units and preserved stroma with mild congestion of some renal blood vessels and mild dilatation of some proximal and distal convoluted tubules (Fig. 3F).

DISCUSSION

Linezolid is a preferable choice for many patients, not only for its broad activity against gram positive pathogens but also it has 100% bioavailability post its oral application. Linezolid associated deleterious actions including hepatic and renal oxidative disturbances restrict its prolong therapy. In this study we hypothesized that pretreatment with both garlic and Vit E for 14 successive days will adjust LNZ adverse actions and improve its clinical use.

Linezolid toxicity was considered to be the cause of the lactic acidosis (De Bus *et al.,* 2010) which cause damage of the organs as liver and kidneys (Vivekanandan *et al.,* 2018). The damage of hepatocytes causes leakage of the enzymes in the affected tissue and their release into the blood stream (Shaarawy *et al.,* 2009). The serum levels of AST, ALT (indicators of liver function) and serum ALP (indicator of hepatobiliary disease) were unregulated in LNZ treated group indicating liver damage and this confirmed histopathologically. In agreement with animal studies of French, (2003) who demonstrated increases in hepatic transaminase with LNZ treatment which was dose-dependent and reversible.

Treatment with either garlic or Vit E protected the structural integrity of liver and improved most of histopathological changes represented by significant decrease in AST, ALT and ALP. Garlic extract has been shown to decrease liver enzymes in serum and prevent liver damage of rats with liver fibrosis (Nakagawat *et al.,* 1989), due to its ability to reduce free radical-induced oxidative damage in the liver (Gedik *et al.,* 2005). Vitamin E showed a significant decrease in the activity of these enzymes compared to cyclophosphamide treated group (Khanalizadeh and Najafian, 2014).

Urea and creatinine are waste products of protein metabolism, excreted by the kidney and their increase indicate renal function damage (Salem and Salem, 2016). During LNZ treatment, increased rate of LNZ non renal clearance because of decreased renal creatinine clearance. This compensatory increase for LNZ clearance due to enhanced drug biotransformation, biliary excretion, decreased absolute bioavailability, or changes in drug distribution (Brier *et al.,* 2003). The existing study revealed a significant increase in urea which is sensitive indicator of renal abnormalities and that confirmed by histopathological examining, while non significant change in creatinine was observed in LNZ group compared to control groups. The serum creatinine is more sensitive kidney function test than urea (Chauhan *et al.,* 2016). Because of increased creatinine tubular secretion, its serum level does not significantly increased until the glomerular filtration rate is reduced to less than 50% of normal level (Perrone *et al.,* 1992). Urea is not secreted by the tubules, freely filtered by the glomerulus and 40–70% is passively reabsorbed from the renal tubules (Newman and Price, 2005). Moreover, urea level is influenced by health status, feeding and liver function. The data are in accordance with Nukui *et al.* (2013) who reported renal function disturbance at 3rd day of LNZ therapy. Either garlic or Vit E treatment modulated the urea alterations and confirmed by histological results. Garlic contains more than 200 chemical compounds including volatile oil with sulphur containing allicin, allin, ajone, allinase, peroxidase and myrosinase (Block, 1985). Vitamin E up-regulates of phospholipid A2 and cyclooxygenase-1, leads to the release of prostacyclin which improves the GFR and corrects the serum levels of creatinine and urea (Mohammed *et al.,* 2014).

The free radicals play a main role in numerous pathological dysfunctions such as hepatotoxicity, inflammations, diabetes mellitus and cardiovascular disorders (Zwart *et al.,* 1999). SOD is the first enzyme in the antioxidant defense mechanism and CAT protects the cell from oxidative damage induced by H_2O_2 and hydroxyl radical. A significant reduction in CAT and SOD with a significant increase in MDA concentration were reported in LNZ treated rats compared with control groups and garlic or Vit E treatment ameliorates these alterations. The LNZ oxidative stress was previously confirmed by Vivekanandan *et al.* (2018) who reported a significant increase in lipid hydroperoxide and MDA with a significant decrease in SOD, CAT, glutathione reductase (GSSH), peroxidase (Px), and glutathione peroxidase (Gpx). The present findings are in accordance with Zaidi *et al.* (2019) who reported that crude garlic extract significantly increased the hepatic activities of SOD, CAT and glutathione-S transferase (GST). The same results were obtained with aged garlic extract pretreatment in cisplatin treated rats (Nasr, 2014).

Such improvements for garlic are attributed to organosulfur compounds allicin, alliin, S-allyl cysteine (SAC) and S-allylmercaptocysteine (SAMC) which are potent free radical scavengers (Tsai *et al.,* 2012) and (Mellon *et al.,* 2000). Moreover, garlic increased resistance of low density lipoprotein to oxidation which accounts for its antioxidant and anti-atherosclerotic functions (Lau, 2001). Vitamin E keeps the integrity of membrane by preventing lipid peroxidation and enhancing the activity of antioxidant enzymes (Abd *et al.,* 2016). The antioxidant effect of Vit E is depend on the presence of a hydroxyl group in its phenolic group on the chromanol ring which can donate a hydrogen atom and, subsequently, neutralize the free radicals (Wang and Quinn, 1999).

CONCLUSIONS

This study was the first report to evaluate the protective effect of garlic or Vit E against LNZ induced hepato- renal oxidative stress. Linezolid induced biochemical disturbances and altered oxidative status and both garlic and Vit E restored liver and kidney function biomarkers and reestablished the antioxidant/oxidant condition. We recommend using either Vit E or garlic as a supplement to alleviate LNZ undesirable actions.

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التأثير التحسينى للثوم الطازج وفيتامين هـ ضد الأضرار المؤكسدة الكبدية والكلوية المستحثة باللينزوليد في الجرذان

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أجريت الدراسة الحالية للمقارنة بين التأثير الوقائي لكل من الثوم أو فيتامين هـ ضد التلف الكبدي والكلوي الناجم عن تجريع ١٠٠ مليجرام/كجم لينزوليد. تم تقسيم ثلاثين من ذكور الجرذان البيضاء إلى ست مجموعات متساوية: المجموعة الاولى لم تلق أى معالجة. بينما المجموعة الثانية والثالثة تلقت توين ٨٠ وزيت الزيتون عن طرق الفم. تم تجريع اللينزوليد للمجموعة الرابعة (١٠٠مليجرام/كجم). أما عن المجموعتين الأخيرتين تم إعطاءهم إما الثوم (٥٠٠مليجرام/كجم) أو فيتامين هـ (١٠٠مليجرام/كجم) قبل إعطاء اللينزوليد بساعة يوميا لمدة أربعة عشر يوما متتالياً. تم الحصول على عينات دم من جميع الجرذان لإجراء فحوصات كيميائية حيوية ومؤشرات حيوية للتأكسد كما تم إستئصال عينات من الكبد والكلى لفحص الأنسجة. أظهرت النتائج وجود إرتفاع كبير في مصل الأسبارتات أمينوترانزفيراز (AST) ، ألانين أمينوترانزفيراز (ALT) ، الفوسفاتيز القلوي (ALP) واليوريا فى المجموعة المعطاة اللينزوليد. كما لوحظ وجود تغييرات في حالة مضادات الأكسدة / حالة التأكسد أثناء تناول اللينزوليد. قام كل من الثوم وفيتامين هـ بتحسين التغييرات الكيميائية والهستوباثولوجية. لذا فإن كل من الثوم وفيتامين هـ قادرين على تحسين التغييرات التي يحدثها اللينزوليد عبر آثارهم المضادة للأكسدة.