



**ORIGINAL ARTICLE**

# The Possible Protective Role of N-acetyl Cysteine Against Tamoxifen-induced Hepatotoxicity in the Adult Female Albino Rats: Biochemical and Histological Study

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## ABSTRACT

**Background:** Tamoxifen is a commonly used anticancer drug acting as a selective estrogen receptor blocker so, used primarily for prophylaxis of breast cancer in high risk women and the treatment of breast malignancies in both males and females. N-acetylcysteine is a well-known drug with strong antimicrobial, antioxidant, mucolytic anti-inflammatory properties hence; it's used as an effective drug for protection against numerous toxic substances. The current study aimed to evaluate the protective effects of N-acetylcysteine against tamoxifen-induced hepatotoxicity in the adult female albino rats.

**Methods:** Sixty adult female albino rats were used in the current study. The rats were randomly divided into 4 groups with 15 rats in each group; group 1 received only the standard food and distilled water, group 2 received N-acetylcysteine in a daily dose of 150 mg/kg, group 3 received tamoxifen in a daily dose of 45 mg/kg and group 4 received tamoxifen and N-acetylcysteine daily for 6 successive weeks. At the end of the experiment, blood samples and livers were collected for biochemical and histological evaluation.

**Results:** Tamoxifen administration resulted in obvious hepatotoxic effects in the form of marked elevation of the serum liver enzymes, disturbance of the antioxidant liver tissue capacity and distortion of the liver architecture with congestion, portal fibrosis and disarrangement and increased apoptosis affecting the hepatocytes. N-acetylcysteine co-treatment ameliorated all the biochemical and histological hepatotoxic effects of tamoxifen.

**Conclusions:** N-acetylcysteine has effective properties against the hepatotoxic effects induced by tamoxifen so, it is useful to be given to the high risk women.

**Keywords:** N-acetylcysteine; Tamoxifen; Hepatotoxicity; Rats.



## INTRODUCTION

The liver is a vital organ that lies in the upper part of the abdomen immediately below the diaphragm. It occupies the greater part of the right hypochondrium and extends across the epigastrium to reach the left hypochondrium[1]. The liver represents the largest gland in the human body and acts as a mixed gland; endocrine and exocrine. The endocrine part secretes essential proteins including prothrombin, albumin and fibrinogen into the blood stream directly while the exocrine part secretes the bile into the small intestine through the biliary passages[2].

Moreover, the liver is involved in the metabolism of fatty acids, formation of lipoproteins, phospholipids and cholesterol. It

also shares in carbohydrates metabolism including the formation and storage of glycogen[3]. In addition, it is essential for removal of toxins and chemicals from the body because it receives the chemical drugs and toxins absorbed from the intestine through the portal vein[4].

Hepatic impairment diseases are among the leading causes of death all over the world representing a public health problem[5]. Drug-induced hepatotoxicity is among the common causes of hepatic diseases and results from the side effects of certain drugs on the liver cells[6].

Tamoxifen (TAM) is a non-steroidal competitive anti-estrogen agent. TAM is used mainly as the drug of first choice for the treatment of the estrogen-dependent breast

cancer and also, used as a prophylactic agent against breast cancer in the high risk women[7]. It produces its anti-estrogenic properties by blocking the estrogen receptors, therefore prevents the action of estrogen required for the growth of the estrogen receptor-positive breast cancers[7].

In spite of being effective in the treatment and prophylaxis of breast malignancies, prolonged administration of TAM is potentially accompanied by hepatic damage. It causes liver injury through induction of oxidative stress and inflammation in the liver[8]. There is a wide spectrum of TAM-induced liver injuries including hepatitis, hepatic necrosis, hepatic steatosis, cirrhosis and hepatocellular malignancies[8]. The mechanisms of TAM-induced hepatic damage include suppression of  $\beta$ -oxidation of the fatty acids and formation of dicarboxylic acid with subsequent mitochondria damage through the activation of alternative fatty acid oxidation pathway rather than  $\beta$ -oxidation[9]. Mitochondrial damage induced by TAM leads to excessive production of reactive oxygen species that enhance lipid peroxidation of the fatty acids leading to liver damage[9].

N-acetylcysteine (NAC) is a widely used drug synthesized by addition of acetyl group to L-cysteine that is a naturally occurring amino acid[10]. NAC has antioxidant, anti-inflammatory, immunomodulatory, antimicrobial[11] and mucolytic properties[12]. It induces its antioxidant properties directly by inhibition of certain oxidant species such as hydroxyl, nitrogen dioxide and hydrogen peroxide and indirectly by acting as a precursor for the strong antioxidant glutathione (GSH)[11]. Because of its antioxidant capacity, NAC is proposed to treat oxidative stress-induced liver injury[10] as in cases of acetaminophen toxicity[13]. It inhibits the strong pro-inflammatory nuclear factor (NF)- $\kappa$ B and reduces the other pro-inflammatory factors such as cytokines and chemokines[11]. It induces its mucolytic role through destruction of the high-molecular-weight glycoproteins of the mucus leading to reduced mucus viscosity for easy coughing and expectoration[12,13].

NAC is used as an effective drug for the management of hepatic injuries either acute or

chronic[14]. Its ability to counteract the acute liver injury is due to its capacity to improve oxygenation and perfusion of the liver cells during the shock-like stage through its inotropic and vasodilatory properties. Moreover, in the management of acute and chronic liver injuries, NAC antagonizes the oxidizing properties of the free oxygen radicals and increases the level of the mitochondrial and cytoplasmic GSH stores by acting as a GSH precursor[14].

## METHODS

### *Site of the study:*

This study was carried out in Animal house, Medical research center, Faculty of Medicine, Ain Shams University, Cairo; Histology Department, Faculty of Medicine, Al-Azhar University, Cairo and Electron microscope unit, Al-Azhar University, Cairo.

### *Chemicals:*

Tamoxifen, N-acetylcysteine, 1.1% isoflurane, Monoclonal antibodies against NF- $\kappa$ B, normal saline and distilled water were purchased from Sigma-Aldrich Co (St. Louis, MO, USA).

### *Animals:*

Sixty adult female albino rats of 6 months age and 200-260 gm weight were bought from the breeding unit of the animal health research institute in Dokki, Egypt. Along the experiment, the rats were kept in a pathogen-free environment. The rats were placed inside plastic cages under standard laboratory conditions of lighting, humidity and temperature in the animal house of the center of researches, Faculty of human Medicine, Ain Shams University. Along the experiment, the rats were fed balanced diet and tap water. The animals were used according to the code of ethics of the experimental researches guidelines adopted by Ain Shams University with a code number in the experimental animal research unit of [RE(100)22].

The period of the experiment: The total period of the experiment was 4 weeks. The first one week was for acclimation only during which the animals were kept in the environment of the experiment and only received balanced meals and tap water. The last 3 weeks were for treating the rats with the chemicals of the study in addition to the ordinary nutrition.

### *Study design:*

After the period of acclimation (the first one week), the rats were randomly divided into four equivalent groups (15 rats in each group put in 3 separate cages, 5 animals in each cage) and treated around 9 am for successive 3 weeks as follows:

**Group 1 (control group):** Received only basal diet and tap water.

**Group 2 (NAC-treated group):** Received N-acetylcysteine in a dose of 150 mg/kg dissolved in distilled water orally by gastric gavage[15].

**Group 3 (TAM-treated group):** Received TAM dissolved in normal saline by intraperitoneal injection in a daily dose of 45 mg/kg[16].

**Group 4 (TAM and NAC-treated group):** Received TAM dissolved in normal saline by intraperitoneal injection in a daily dose of 45 mg/kg[16] and NAC in a dose of 150 mg/kg dissolved in distilled water orally by gastric gavage[15].

#### *Samples collection:*

At the end of the experiment (The end of the 4th week), the rats were anaesthetized by inhalation of 1.1% isoflurane[17]. The blood samples were collected by introducing the needle through the medial angle of the orbit then, the blood was obtained from the retro-orbital venous plexus. After collecting the blood samples, the rats were euthanized by cervical decapitation, the anterior abdominal wall was dissected and liver samples were collected from all rats[18].

#### *Biochemical analysis:*

##### **i- Assessment of liver function enzymes:**

The serum was separated by centrifugation of the blood samples at 3000 rpm for 10 minutes. Then, the serum stored at -20°C and assessed for serum aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH)[19].

##### **ii- Assessment of oxidative stress in liver tissue:**

Parts of the liver specimens of each group were stored at -80°C then, malondialdehyde (MDA) and Glutathione (GSH) levels were measured in the liver tissue by homogenization to evaluate the oxidant/antioxidant status[19].

#### *Histological evaluation of the liver tissue:*

Ten liver specimens of each group were fixed in 10% neutral-buffered formalin solution then, processed for histopathological and immunohistochemical examinations.

**i- Haematoxylin and eosin:** For morphological assessment of the state and detection of the degenerative changes of the liver[20].

**ii- Masson's trichrome stain:** Slides were stained by Masson's trichrome stain to detect the amount of collagen fibers in the liver specially in the portal tract[21].

**iii- Immunohistochemistry:** Antibodies against the p65 subunit of the activated nuclear factor kappa B (NF-κB) were used to detect NF-κB p65 positive destroyed hepatocytes. The sections were incubated with primary monoclonal rabbit antibodies to p65 (1:1000; Cell

Signaling Technology, Boston) at 4 °C overnight then, washed with Tris buffer saline with 0.1% Tween 20 (TBST) and incubated with secondary peroxidase-conjugated goat anti-mouse IgG antibodies (1:5000; Santa Cruz Biotechnology, Dallas) for 2 hours at room temperature. Finally, the slides were stained by NF-κB immunostain then examined by light microscope[22].

**iv- Electron microscopy:** About 1 mm<sup>3</sup> size pieces of the liver specimens were taken from all groups. These pieces were fixed in 2% gluteraldehyde in 0.1 mol/l phosphate buffered solution at pH 7.4 for two hours then, gradually dehydrated using ascending concentrations of ethyl alcohol. The specimens then put in a mixture of propylene oxide and resin then, capsulated in BEEM and ultrathin sections were taken by the ultramicrotome. The sections were stained by lead citrate and uranyl acetate and examined by the transmission electron microscope[23].

#### *Statistical analysis:*

The findings were processed and presented in the form of means ± SD (Standard deviation). The data were statistically analyzed by SPSS statistics version 7.7 through the t test to compare the means of each 2 groups and one-way analysis of variance (ANOVA) to compare the variances across the means of all groups. P-values < 0.05 were considered as statistically significant differences[24].

**RESULTS**

**A- Biochemical results:**

**i- Effects on the liver function enzymes:**

There was non-significant difference in the mean values of the serum levels of all measured liver enzymes; ALT, AST, ALP and LDH between groups 1 and 2 (the control group and NAC-treated group) however, there was a significant increase in their levels in group 3 (the TAM-treated group) in comparison to the control group. Group 4 showed a significant decrease in the mean values of these enzymes when compared to group 3 and non-significant differences when compared to the control groups (Fig. 1, table 1).

**ii- Effects on the oxidant/antioxidant status markers:**

There was no significant difference in MDA and GSH levels in the liver tissue between groups 1 and 2 however, there were significantly increased MDA and decreased GSH levels in group 3 when compared to the control group. Group 4 showed significantly decreased MDA and increased GSH levels when compared to group 3 but when compared to the control group, the level of GSH showed non-significant difference while the MDA concentration was significantly increased (Fig. 1, table 1).

**B- Histological results:**

**i- Haematoxyline and eosin stained sections:**

Group 1 and group 2 showed average portal tracts, average portal veins, and average central veins, average blood sinusoids and average hepatocytes in the peri-portal and peri-venular areas. Group 3 showed edematous portal tracts, markedly dilated

congested portal veins, markedly dilated congested central veins and disarranged apoptotic hepatocytes in the peri-portal and peri-venular areas. Group 4 showed average portal tracts, average portal veins, average central veins and average hepatocytes in the peri-portal and peri-venular areas (Figures 2-3).

**Masson trichrome stained sections:**

Groups 1 and 2 showed average collagen fibers distribution in the portal tracts. In group 3, TAM resulted in excess collagen fibers while in group 4, co-administration of NAC resulted in the presence of average collagen fibers in the portal tracts (Figure 4).

**NF-κB immuno-stained sections:**

Groups 1 and 2 showed negative cytoplasmic reactivity against NF-κB p65. In group 3, TAM administration resulted in positive NF-κB p65 cytoplasmic reactivity while in group 4, co-administration of NAC resulted in negative cytoplasmic reactivity (Figure 5).

**Electron microscopy sections:**

The control and the NAC-treated groups showed regular hepatocytes with regular nuclei containing homogenously dispersed chromatin, regular mitochondria, regular Golgi apparatus and rough endoplasmic reticula. The TAM-treated group showed irregular hepatocytes with irregular nuclei containing clumped chromatin, distended mitochondria with destroyed cristae and numerous cytoplasmic vesicles. In the TAM and NAC-treated group, the hepatocytes were regular with regular nuclei containing homogenously dispersed chromatin, numerous regular mitochondria, regular Golgi apparatus and rough endoplasmic reticula (Figure 6).

**Table 1.** The mean values of the liver function enzymes in the serum and the oxidant/antioxidant status markers in the liver tissue in the four groups.

	Group 1		Group 2		Group 3		Group 4		P value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
AST (U/L)	15	1	17	2 <sup>a</sup>	73	3 <sup>b</sup>	20	2 <sup>ac</sup>	<0.007
ALT(U/L)	14.9	2.81	15.4	2.17 <sup>a</sup>	60.70	5.06 <sup>b</sup>	17.20	3.12 <sup>ac</sup>	<0.004
ALP(U/L)	131.2	6.75	138.7	8.68 <sup>a</sup>	304.50	12.20 <sup>b</sup>	143.4	7.31 <sup>ac</sup>	<0.001
LDH(U/L)	79.7	2.06	72.60	1.84 <sup>a</sup>	193.80	12.04 <sup>b</sup>	86.40	6.79 <sup>ac</sup>	<0.001

	Group 1		Group 2		Group 3		Group 4		P value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
GSH (nmol/mg)	61.4	5.76	57.7	9.46 <sup>a</sup>	18.70	3.13 <sup>b</sup>	55.20	7.61 <sup>ac</sup>	<0.003
MDA (nmol/mg)	5.80	1.62	5.9	1.20 <sup>a</sup>	43.40	5.25 <sup>b</sup>	11.60	2.12 <sup>ac</sup>	<0.007

\* P value was calculated by one way ANOVA test

P value > 0.05 means non-significant results

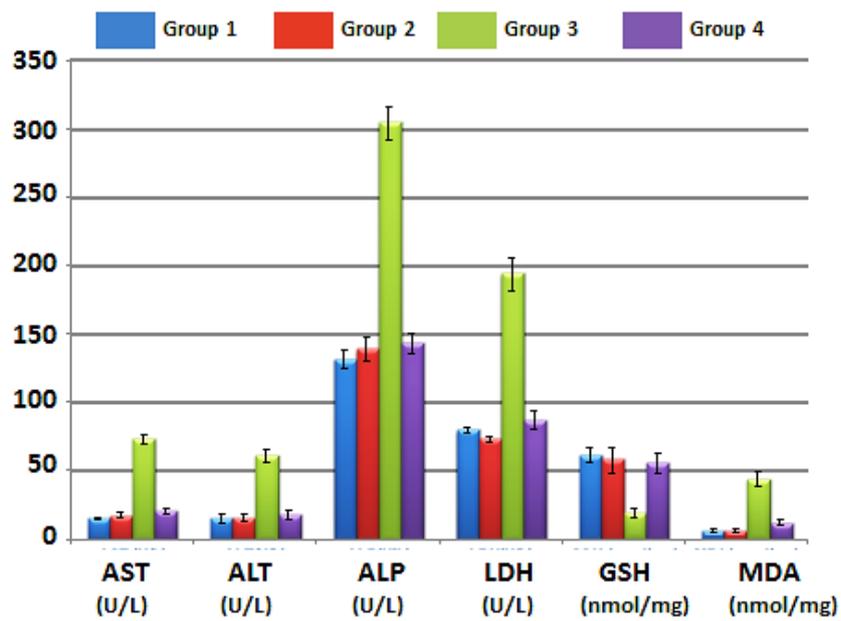
P value < 0.05 means significant results

\* The data were represented in mean ± SD (Standard deviation)

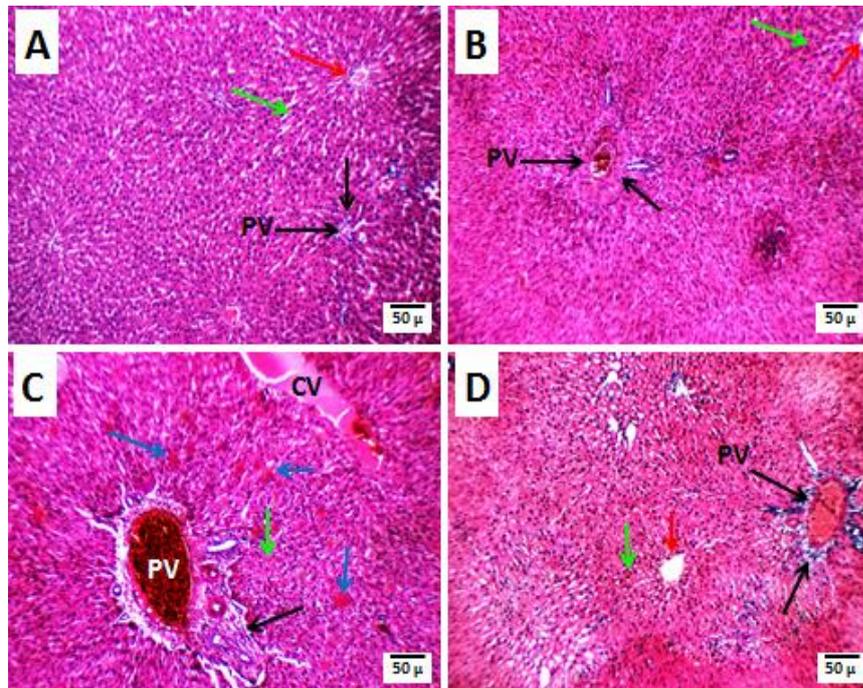
a = Non-significant when compared to the same parameter in group 1 (P > 0.05)

b = Significant when compared to the same parameter in group 1 (P < 0.01)

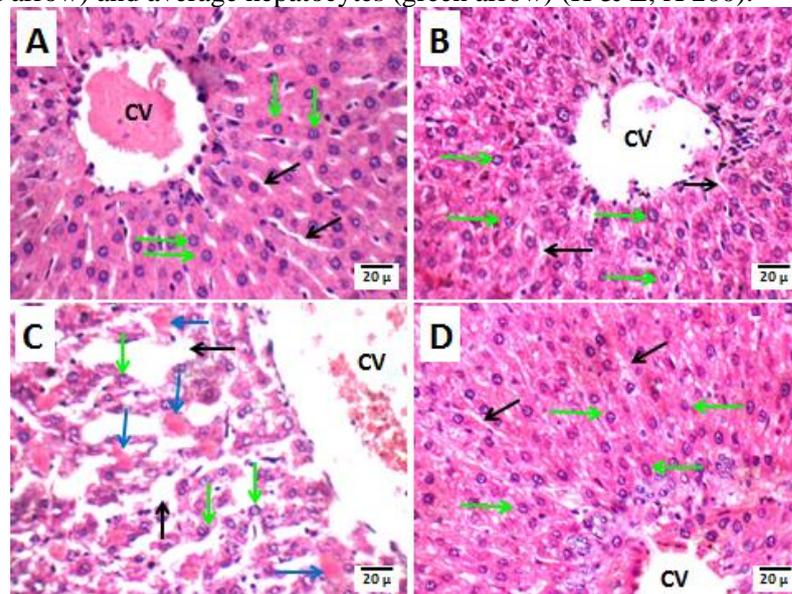
c = Significant when compared to the same parameter in group 3 (P < 0.01)



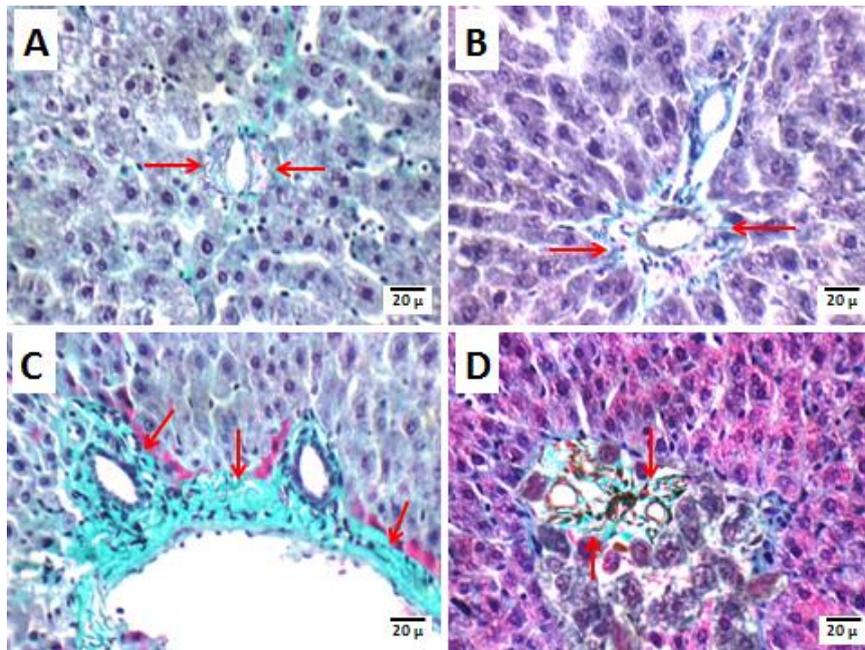
**Figure 1:** The mean level values of the liver function enzymes; aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) in the serum and the mean level values of the oxidant/antioxidant status markers; malondialdehyde (MDA) and Glutathione (GSH) in the liver tissue.



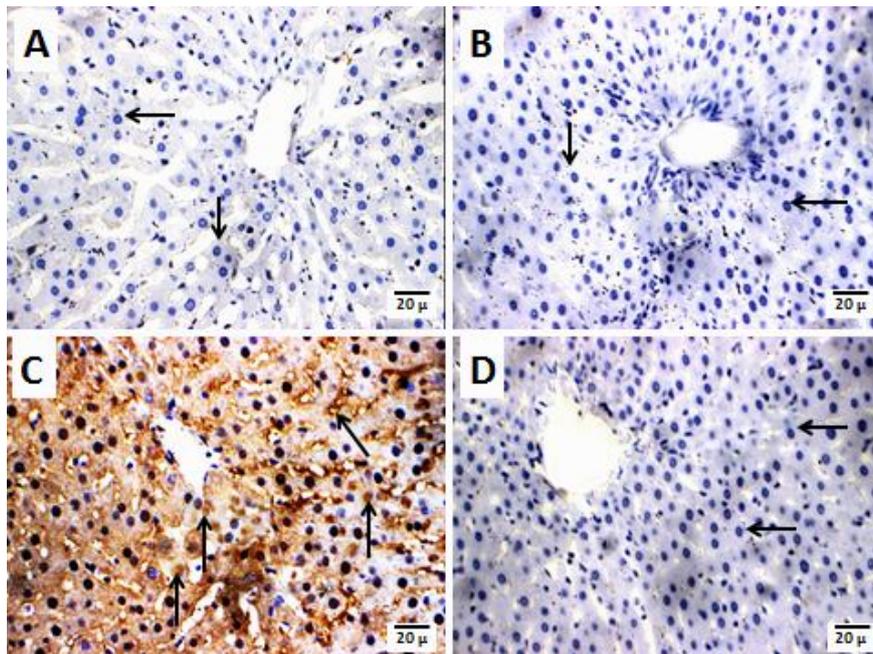
**Figure 2:** The control group (photomicrograph A) and the NAC-treated group (photomicrograph B) show the average appearance of the liver tissue with average portal tract (black arrow), average portal vein (PV), average central vein (red arrow) and average hepatocytes (green arrow). The TAM-treated group (photomicrograph C) shows edematous portal tracts (black arrow), markedly dilated congested portal vein (PV), markedly dilated congested central vein (CV), disarranged hepatocytes (green arrow) and numerous apoptotic bodies (blue arrows). The TAM and NAC-treated group (photomicrograph D) shows average portal tract (black arrow), average portal vein (PV), average central vein (red arrow) and average hepatocytes (green arrow) (H & E; X 200).



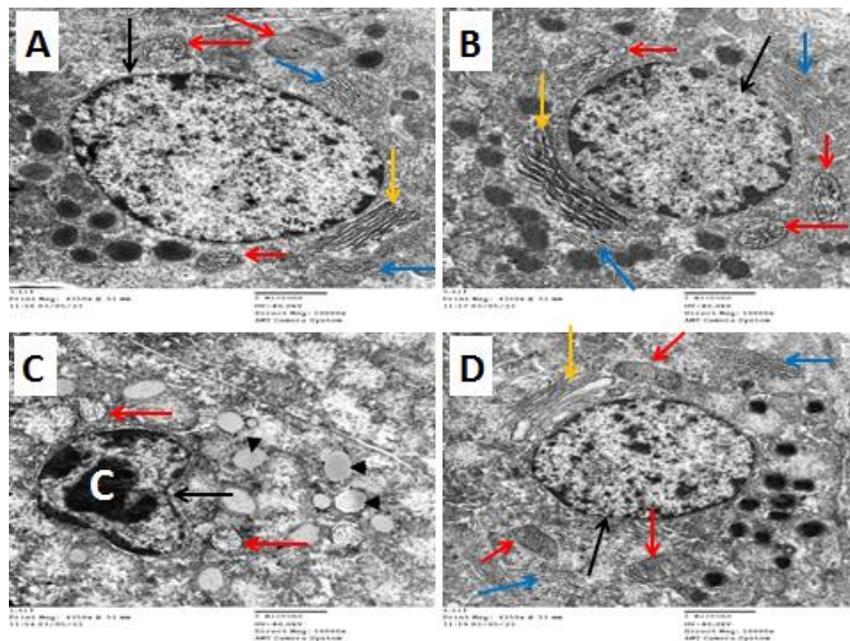
**Figure 3:** The control group (photomicrograph A) and the NAC-treated group (photomicrograph B) show average central veins (CV), average blood sinusoids (black arrows) and average well-arranged hepatocytes (green arrows). The TAM-treated group (photomicrograph C) shows markedly dilated congested central vein (CV), dilated blood sinusoids (black arrows), scattered disarranged hepatocytes (green arrow) and numerous apoptotic bodies (blue arrows). The TAM and NAC-treated group (photomicrograph D) shows average central vein (CV), average blood sinusoids (black arrows) and average well-arranged hepatocytes (green arrows) (H & E; X 400).



**Figure 4:** The control group (photomicrograph A) and the NAC-treated group (photomicrograph B) show average green stained collagen fibers distribution in the portal tracts (red arrows). The TAM-treated group (photomicrograph C) shows excess collagen fibers (red arrows) while the TAM and NAC-treated group (photomicrograph D) shows average collagen fibers distribution in the portal tract (red arrows) (Masson's trichrome X 400).



**Figure 5:** The control group (photomicrograph A) and the NAC-treated group (photomicrograph B) show negative cytoplasmic reactivity for NF- $\kappa$ B p65 (arrows). The TAM-treated group (photomicrograph C) shows positive cytoplasmic NF- $\kappa$ B p65 reactivity indicated by the presence of numerous dark brown stained hepatocytes (arrows). The TAM and NAC-treated group (photomicrograph D) shows negative cytoplasmic reactivity (arrows) (NF- $\kappa$ B immunostain X 400).



**Figure 6:** The control group (photomicrograph A) and the NAC-treated group (photomicrograph B) show regular hepatocytes with regular nuclei (black arrows) containing homogenously dispersed chromatin, regular mitochondria (red arrows), regular Golgi apparatus (yellow arrows) beside the nucleus and rough endoplasmic reticula (blue arrows). The TAM-treated group shows irregular hepatocytes with irregular nucleus (black arrow) containing clumped chromatin (C), distended mitochondria (red arrows) with destroyed cristae and numerous cytoplasmic vesicles (heads of arrows) representing degenerated organelles. In the TAM and NAC-treated group, the hepatocytes are regular with regular nuclei (black arrows) containing homogenously dispersed chromatin, numerous regular mitochondria (red arrows), regular Golgi apparatus (yellow arrows) and rough endoplasmic reticula (blue arrows) (X 10000).

### DISCUSSION

Tamoxifen is commonly used as an effective drug for the management of the estrogen-dependent malignant breast tumors that result from non-counteracted effects of estrogen on the breast tissue[25]. Prolonged TAM administration for 5 years significantly increases the 5-years survival rate, especially in females after the menopause[26]. However, numerous previous studies proved that, the prolonged use of TAM is limited by the possible appearance of numerous undesirable side effects including vaginal dryness, sleep disturbances, hot flushes, loss of sexual desire, depression and weight gain[27]. Moreover, previous results detected that, administration of TAM for a long period can induce hepatotoxicity that is one of the most serious side effects[28]. In the present study, we evaluated the effectiveness of NAC to prevent and control the liver injury induced by TAM through biochemical and histological methods with a hope for the possible effective use of NAC in the high risk

patients to prevent the TAM-induced hepatotoxicity.

In the present study, the serum levels of liver enzymes; AST, ALT, ALP and LDH were markedly elevated in the TAM-treated group in comparison to the control group. Also, TAM administration resulted in disturbed hepatic oxidant/antioxidant balance detected by increased MDA and decreased GSH levels in the liver tissue. These biochemical results indicated TAM-induced liver cell destruction and this was more confirmed by histological liver examination that detected hepatic degeneration. On the other hand, concurrent administration of NAC significantly alleviated the hepatotoxic effects of TAM. The hepatoprotective effects of NAC against the TAM-induced hepatotoxicity were detected by significant remission of the serum liver enzymes, decrease of MDA and increase of GSH levels in group 4 in comparison to group 3. The levels of these markers in group 4 became near the corresponding values in the control group denoting NAC-mediated

restoration of the antioxidant capacity and amelioration of lipid peroxidation when NAC was co-administered with TAM. This hepatoprotective potency of NAC against TAM was more confirmed by histological liver assessment that detected alleviation of the degenerative hepatotoxic changes in group 4 when compared to group 3.

The findings of the present study were in line with previous studies detected elevated liver enzymes and destroyed liver cells in rats exposed to TAM[29]. The serum levels of the liver enzymes indicated the degree of hepatic damage and function disturbance because these enzymes resulted from their leakage from the destroyed hepatocytes into the blood stream[30]. According to previous studies, these results indicated severe TAM-induced oxidative stress and disturbance of the oxidant/antioxidant balance. MDA is a main product of the oxidation of the polyunsaturated fatty acids so, its elevation denoted increased lipid peroxidation (LPO) of the cell membrane. GSH is a strong antioxidant so, its decrease indicated impaired antioxidant capacity of the liver tissue[31,32]. The hepatoprotective effects of NAC against TAM-mediated hepatotoxicity detected in the present study were in correlation with numerous previous studies. These hepatoprotective effects of NAC were attributable to its antioxidant potency that counteracts the liver injuries caused by toxins-mediated oxidative stress[33]. According to previous results, NAC elicits its antioxidant capacity through amelioration of lipid peroxidation of the cell membrane and enhancement of the antioxidant capacity[34]. It was previously detected that, NAC has strong antioxidant effects by acting as a direct antioxidant in addition to its role as a precursor for GSH that provides more antioxidant capacity[35].

In the current study, the TAM-induced degenerative histological changes of the liver were detected by the presence of disarranged and apoptotic liver cells, dilatation of the blood sinusoids and congestion of the central and portal veins with excessive portal fibrosis in group 3 in comparison to the control group. These findings were in correlation with the results of previous studies detected similar

hepatotoxic effects of TAM[36]. The efficacy of NAC to reverse the TAM-induced histological hepatotoxic effects detected in the present study was in agreement with previous results proved that, NAC co-administration was effective in preservation of the average histological pattern against toxins-induced hepatotoxicity[37,38].

In the present study, the ultrastructural findings detected in the liver cells in group 3; irregular nuclei with clumped chromatin, swollen mitochondria, cytoplasmic vacuoles and absent organelles denoted TAM-induced ultrastructural hepatodegenerative changes. These findings were in agreement with previous results detected that, TAM-induced oxidative stress leads to destruction of mitochondria with subsequent cessation of energy generation leading to multiple deleterious effects that destroy the hepatocytes[39]. On the opposite side, the current study detected the effectiveness of NAC to ameliorate these TAM-induced ultrastructural changes. This was in correlation with previous results proved that, NAC has a mitochondrial protective effect that prolongs the cell life of the hepatocytes and preserves their organelles against the hepatotoxic agents. The NAC-mediated mitochondrial protection prolongs the cell life because mitochondria are the main source of the energy required for cell survival[40].

In conclusion, the present study showed that, NAC has a protective role against TAM-induced hepatotoxicity so, it is valuable to prescribe NAC to patients receiving tamoxifen for prolonged periods

**Conflicts of interest:** None

**Financial disclosure:** None

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