

# Sodium Butyrate Attenuates Nephrotoxicity Induced by Tamoxifen in Rats

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## ABSTRACT

Tamoxifen (TAM) is a hormonal selective estrogen modulator used in the prevention and treatment of breast cancer. It associated with increased in the oxidative stress in cells leading to tissue injury. Sodium butyrate (NaBu) increased the glutathione redox system and diminished the oxidative stress. The purpose of this study was to elucidate the ameliorative effect of NaBu against TAM-induced kidney injury by reducing the generation of oxidative stress. Rats were divided mainly into four group as follow: control, rats received saline for 14 days orally then saline intraperitoneally (i.p.) for 7 days, NaBu, rats received saline orally for 14 days, NaBu (300mg/kg) (i.p.) for 7 days, TAM, rats received TAM (40mg/kg) orally for 14 days, then saline (i.p.) for 7 days, (TAM-NaBu) rats received TAM orally for 14 days, NaBu (i.p.) for 7 days. Kidney injury followed by TAM treatment was assessed by the elevation in the levels of creatinine, urea, uric acid and MDA and reduction in some oxidative biomarkers, in addition to the abnormal architecture of the kidney. Conversely, Administration of sodium butyrate could ameliorate all of these damaging effects in the antioxidant system in the TAM-treated group. NaBu affords significant increments in the antioxidant enzymes. In addition, it has the therapeutic capacity to protect the kidney from the oxidative stress induced by TAM through improving the kidney function and diminishing the free radicals. Supplementation of NaBu could be useful in alleviating TAM-induced kidney injury.

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## INTRODUCTION

Tamoxifen (TAM) is the most recommended breast anticancer oral medication for prevention and treatment of breast cancer for both men and women (Shukla *et al.*, 2016). Tamoxifen is a hormonal selective estrogen modulator and its Pharma-cological effects are based on its binding to estrogen receptors and suppressing epithelial proliferation of different cell types that lack estrogen receptor (McDonnell, 1999; Johnston 2005). While, TAM could reduce breast cancer disease in high-risk women by 49%, a number of studies indicated the TAM caused carcino-genic and genotoxic effects through TAM metabolites by pairing with Estrogen Receptors (ERs) (Lippman and Brown, 1999).

In addition, TAM has an important role in inducing endometrial and liver cancer, thromboembolic disorders in rats and humans (Kärki *et al.*, 2000). The toxicity of TAM concerning multiple organs and tissues is well-established. This toxicity has been attributed to the reduction of the hexose monophosphate shunt and the treatment with TAM increasing the incidence of oxidative stress in cells leading to tissue injury (Tabassum *et al.*, 2007). Generally, the kidney is considered as the vital organ to eliminate drugs, toxins and endogenous metabolites (Torres, 2008). Previously, it was reported that carcinogenicity of TAM is attributed to its metabolites covalently bind to DNA, resulting in DNA adduct formation in the kidney (Li *et al.*, 1997). In addition, Antineoplastic agents or adjuvant treatments including TAM are directly caused a reduction in renal functions (Kintzel and Dorr 1995). It was suggested that oxidative stress might trigger the pathogenesis of TAM-induced toxicity (Dragan *et al.*, 1996).

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Zuhair (2011), elucidated the possible mechanism of TAM-induced nephrotoxicity. He reported that nephrotoxicity might be due to the Reactive oxygen species (ROS) produced by TAM could damage the glutathione redox system of the kidney and subsequently, induce free radicals production in renal tissue.

Furthermore, ROS generated by TAM, exceeding the antioxidant capacity so triggering cell injury and decreases its ability to detoxify ROS (Zuhair 2011). ROS such as superoxide anions ( $O_2^-$ ), hydroxyl radical (OH $\cdot$ ), and hydrogen peroxide ( $H_2O_2$ ) are important mediators of tissue injury (Saad and Al-Rikabi 2002). ROS generated in the cells by TAM can be scavenged by an antioxidant defense system, such as the glutathione redox system which includes, reduced glutathione (GSH), glutathione peroxidase (GPx), and glutathione-S-transferase (GST) (Halliwell 2007). Antioxidants play an essential role in defending the body from oxidative stress at a cellular level. Therefore, improving the antioxidant system is the principle target to diminish the nephrotoxicity induced by TAM. Several natural products and some synthetic substances display antioxidants impact that affords protection against free radical induced renal damage.

Sodium butyrate is a natural 4-carbon short chain fatty acid that synthesized by the microflora in the colon and functions as the primary source of energy for colonocytes (Liu *et al.*, 2016). In addition, it is known as histone deacetylase inhibitors. Butyrate inhibits cell proliferation and causes differentiation in many tumorous and non-tumorous cells (Niki *et al.*, 1999). It was assumed that the modulation of the glutathione transferase gene may protect cells from genotoxic carcinogens, such as  $H_2O_2$  and 4-hydroxynonenal (Canani, Di Costanzo, and Leone 2012). The mechanism proposed of sodium butyrate is the transcriptional upregulation of detoxifying enzymes, such as GST. Recent studies (Yang *et al.*, 2014; Liu *et al.*, 2016) indicated that sodium butyrate exerts anti-inflammatory effect is through the inhibition of the expression of inflammatory mediators such as nuclear factor-kappa B (NF- $\kappa$ B), tumor necrosis factor alpha (TNF- $\alpha$ ) and interferon-gamma (IFN- $\gamma$ ). The ability of sodium butyrate to exert its antioxidant effect by affecting DNA repair systems and activities of enzymatic or non-enzymatic antioxidants (Hamer *et al.*, 2009).

Nonetheless, there is negligible literature on the impact of sodium butyrate using an in vivo rat model. Therefore, the aim of this study was to investigate the therapeutic effect of sodium butyrate against TAM-induced nephrotoxicity in rat.

## MATERIAL AND METHODS

### Chemicals and Reagents

Nolvadex (tamoxifen citrate 40 mg) was obtained from AstraZeneca (Egypt). Sodium butyrate was purchased from Sigma-Aldrich (St. Louis, MO, USA). Kits for all biochemical parameters were purchased from Biodiagnostic Company diagnostic and research reagents (Dokki, Giza, Egypt).

### Experimental Animals

The experimental animals used in this study were male albino rats *Rattus norvegicus* weighing (250-300  $\pm$ 5 g). The animals were purchased from National Research Center (NRC, Giza, Egypt). Animals were given food and water *ad libitum*. Rats were maintained in a friendly environment with a 12 h/12 h light-dark cycle at room temperature (22  $^{\circ}$ C–25  $^{\circ}$ C). Rats were acclimatized to laboratory conditions for 7 days before commencement of the experiment.

### Ethical Consideration

Experimental protocols and procedures used in this study were approved by the Cairo University, Faculty of Science, Institutional Animal Care and Use Committee (IACUC) (Egypt) (CUFS/F/PHY/45/14). All the experimental procedures were carried out in accordance with international guidelines for the care and use of laboratory animals.

### Experimental Design

Rats were divided into 4 groups randomly (n = 6 / group) as follows:

Group 1: **Control group**, treated orally saline for 14 days then injected intraperitoneally (i.p.) with saline for 7 days.

Group 2: **NaBu group**, received orally saline for 14 days then received an (i.p.) dosage of sodium butyrate (300mg/kg) for 7 days.

Group 3: **TAM group**, treated with an oral dosage of TAM (40 mg/kg b. wt.) orally for 14 days followed i.p. administration of saline for 7 days.

Group 4: **TAM-NaBu group**, rats were treated with TAM orally for 14 days followed by sodium butyrate (i.p.) for 7 days. The doses of TAM and NaBu were chosen from previously published reports (Hashiba *et al.*, 2006; Hemieda 2007; Ferrante *et al.*, 2003).

### Animal Handling

At the end of the experiment, rats were euthanized under anesthesia; their blood samples were collected and centrifuged at (3000 r.p.m, 15 minutes). Serum was stored at  $-20^{\circ}$ C until used for biochemical assays.

### Kidney Homogenate Preparation

The left kidney was homogenized (10 % w/v) in ice-cold 0.1M Tris-HCl buffer (pH = 7.4). The homogenate was centrifuged at (3000 r.p.m, 15 minutes) at  $4^{\circ}$ C and the resultant supernatant was used for the biochemical analyses.

### Biochemical Analysis of Kidney Function Test

The levels of renal function markers included creatinine, urea, and uric acid were determined using the appropriate commercially kits (Bio-Diagnostic, Dokki, Giza, Egypt). Serum urea and uric acid were measured according to (Tietz 1995),

serum creatinine was measured according to the method of (Tietz and Andresen 1986).

### Kidney Oxidative Stress Assessment

Malondialdehyde (MDA) (Ohkawa *et al.*, 1979), reduced glutathione (GSH) (Beutler, Duron, and Kelly 1963), catalase (CAT) (Aebi 1984), superoxide dismutase (SOD) (Nishikimi *et al.*, 1972), glutathione peroxidase (GPx) (Paglia and Valentine 1967), glutathione-S-transferase (GST) (Habig, Pabst, and Jakoby 1974) and nitric oxide (NO) (Montgomery and Dymock 1961), were determined using Biodiagnostic assay kits according to the manufacturer's instructions (Bio-Diagnostic, Dokki, Giza, Egypt).

### Histopathological Preparation.

The right kidney was fixed in 10% neutral buffered formalin solution and embedded in paraffin wax blocks. Sections of 5  $\mu$ m thickness were stained with hematoxylin and eosin (H&E) then examined under light microscope for determination of pathological changes (Meyer 1903).

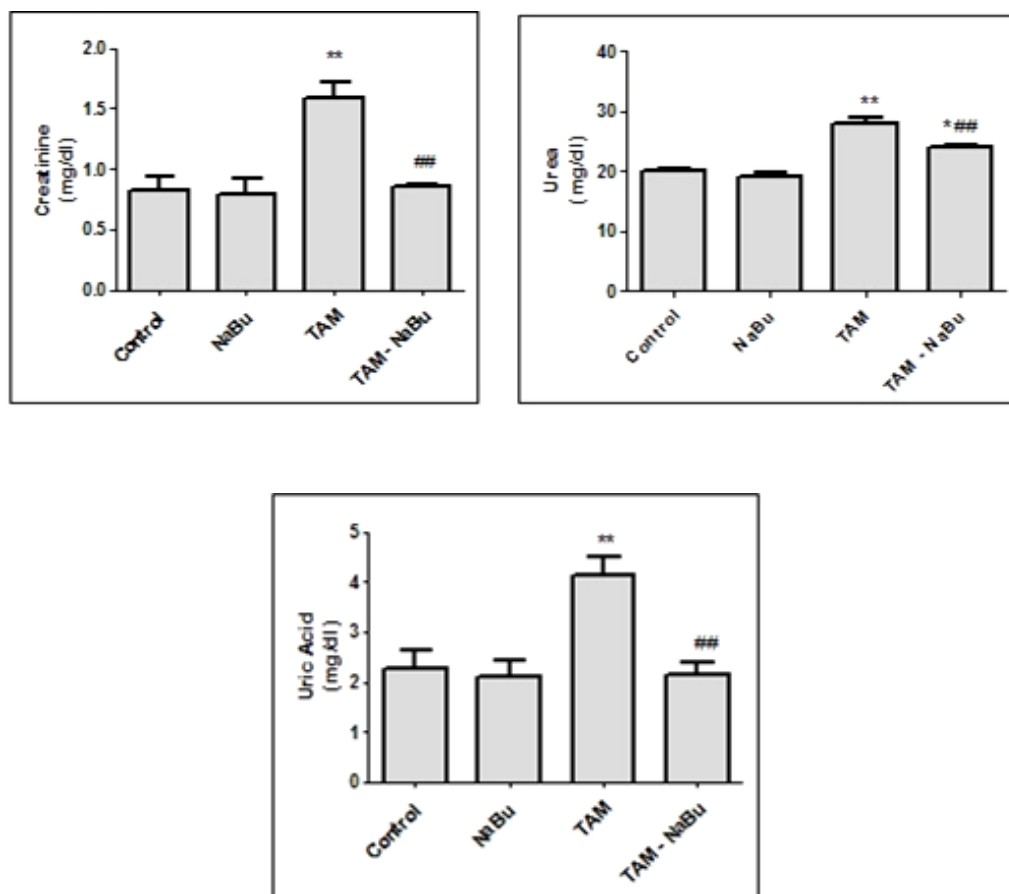
### Statistical Analysis

Data are expressed as mean  $\pm$  SE of six rats in each group. Treated groups are compared with control and TAM group by using Unpaired Student's t-test \* $P < 0.05$ , \*\* $P < 0.01$  vs control group, # $P < 0.05$ ; ## $P < 0.01$  vs TAM. Graph Pad Prism 6 software (Graph PadSoftware, Inc., San Diego, USA) was used for statistical analysis.

## RESULTS

### Kidney function tests

The nephrotoxicity induced by TAM was established by the oral administration of TAM for 14 days. Revealed nephrotoxicity was characterized by a significant increase ( $P < 0.01$ ) in serum creatinine, urea, and uric acid in TAM-treated rats as compared to the control group. On the contrary, treatment with NaBu reversed TAM-induced kidney damage by reducing the levels of creatinine, urea, and uric acid significantly ( $P < 0.01$ ) compared with the TAM group (Figure 1).

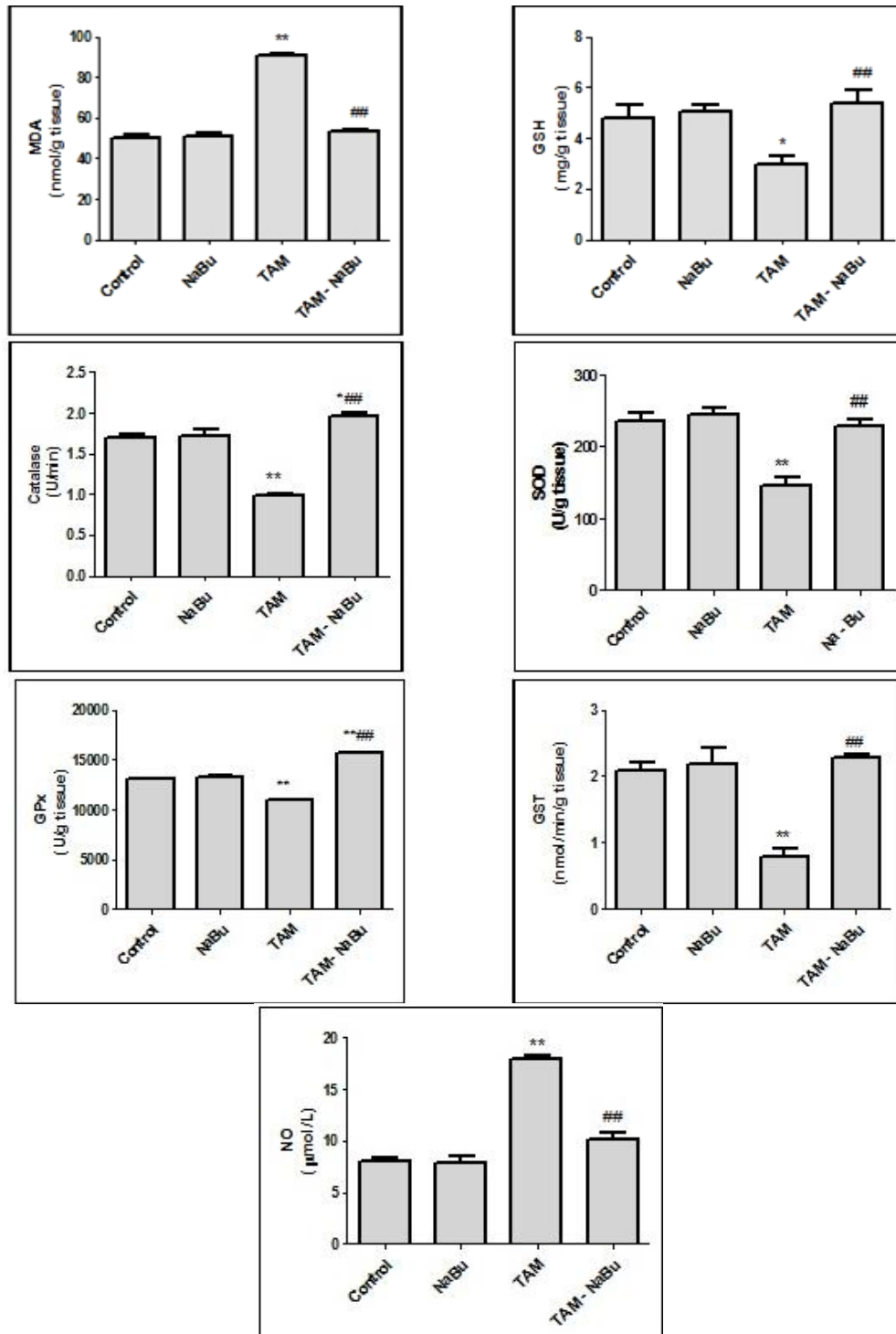


**Fig. 1:** Effect of NaBu on serum urea, uric acid and creatinine of rat treated with TAM. Values are expressed as means  $\pm$  S E (n = 6). Significant difference is indicated by \* $P < 0.05$ , \*\* $P < 0.01$  when compared with control group. Significant difference is indicated by # $P < 0.05$ , ## $P < 0.01$  when compared with TAM group.

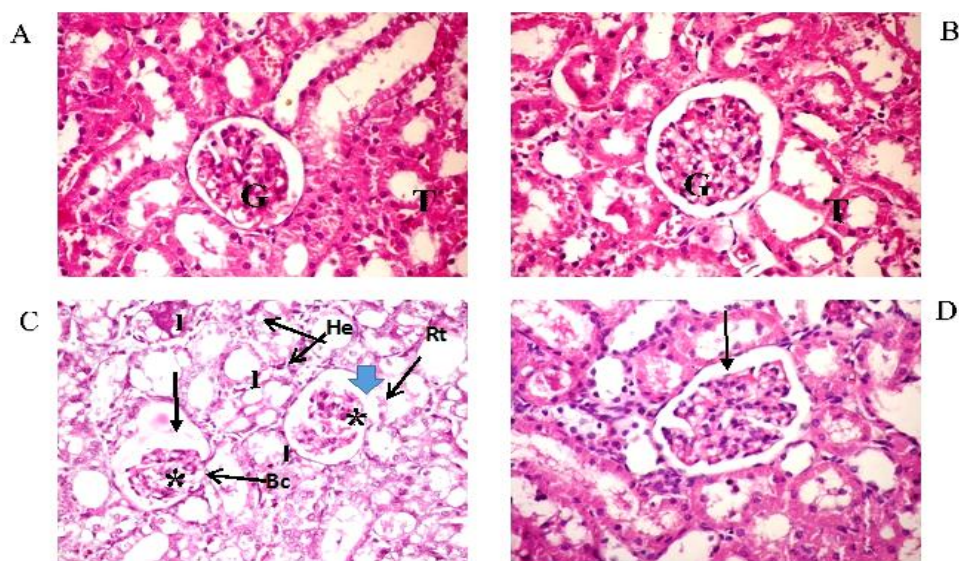
### Renal Oxidative stress biomarkers

Treatment with TAM orally for 14 days caused a significant increase ( $P < 0.01$ ) in MDA and NO concentration of renal tissues, as compared with the control group. TAM weakened the antioxidant defense system by decreasing significantly the GSH ( $P < 0.05$ ), CAT, SOD, GPx, GST ( $P < 0.01$ ) activities in the renal tissues when compared with the corresponding values of

the control group. Treatment with NaBu (TAM-NaBu) was effective in the inhibition of oxidative damage induced by TAM, where it reduced the MDA and NO levels significantly ( $P < 0.01$ ). Moreover, NaBu significantly increases ( $P < 0.01$ ) the renal antioxidant activities such as GSH, CAT, SOD and GPx as compared with TAM group (Figure 2).



**Fig. 2:** Effect of NaBu on enzymatic and non-enzymatic antioxidant in kidney of rat treated with TAM. Values are expressed as means  $\pm$  S E (n = 6). Significant difference is indicated by \* $P < 0.05$ , \*\* $P < 0.01$  when compared with control group. Significant difference is indicated by # $P < 0.05$ , ## $P < 0.01$  when compared with TAM group.



**Fig. 3:** Photomicrographs of renal tissues of Albino rats stained with H&E, x400. (A): Control Group showed normal architecture of renal glomeruli (G), and convoluted tubules (T). (B): Sodium butyrate (NaBu) treated group showed normal structure of renal glomeruli (G) and tubules (T). (C): Tamoxifen (TAM) treated group showed deformation in the renal tissue architecture included congestion in the glomerular capillary tuft (black star); glomerulus (center) appeared shrunken (black arrow) and the epithelium of Bowman's capsule (Bc) appeared degenerated, slight vacuolization in the endothelial cells lining the tuft of the glomeruli (blue arrow), hemorrhage (He) in the renal space and between the convoluted tubules, degenerated epithelium in some renal tubules (Rt) and focal necrosis in other, the renal spaces were significantly reduced and showed inflammatory infiltrate (I). (D): TAM - NaBu-treated group showed slight dilatation of renal tubules (arrow), most of these tubules restore their normal architecture.

### Histopathological Examination of Kidney

The kidney tissue of the control group (Figure 3 A) and NaBu group (Figure 3 B) show the normal architecture of healthy tissue including the normal structure of renal glomeruli and renal tubules. Oral administration of TAM (Figure 3 C) reflects the complications in the architecture of kidney. Where, congestion in the glomerular capillary tuft, slight vacuolization in the endothelial cells lining the tuft of the glomeruli, wide congestion in the glomerular capillary mass, inflammatory cells infiltration, the absence of epithelial cells of renal tubules and deformation in the renal tissue architecture were observed. While, the administration of NaBu as the treatment mediator could restore the healthy morphological and structural shape of the kidney, where the corpuscles and tubules appeared to be similar to those of the control group excepts light dilatation of renal tubules (Figure 3 D). Data from the histological study supports the biochemical analyses and confirmed the TAM has antinephrotoxic activity.

### DISCUSSION

The incidence of kidney failure is mostly associated with the chemotherapy-induced renal dysfunction (Liangos *et al.*, 2006). Kidney damage is irreversible and may lead to the development of end-stage renal disease (Hamad *et al.*, 2015). Lien *et al.* (1991) clarified that the highest levels of TAM and its metabolites were observed in lung, liver, and kidney. There are very few researchers that discuss the effect of TAM on the kidney function tests. Thus, in the present study, we measured the nitrogenous end products; creatinine, urea and uric acid which

reflect the efficacy of kidney function. The present study exposed that the oral administration of TAM for 14 days caused nephrotoxicity, where, creatinine, uric acid, and urea levels were increased. These data are accordance with Ahmed *et al.* (2008) who mentioned that the oral TAM therapy is associated with the damage of kidney function tests which is connected with impairment to the vasculature or/and structures of the kidneys (Ahmed *et al.*, 2008). Oxidative stress is considered as the important factor in the development of a variety of human complications that result from over production of ROS and impairment in the biological defense system (Tabassum *et al.*, 2007). There is increasing evidence that TAM generates ROS production and depletion in the cellular thiol system which are important mediators of nephrotoxicity (Parlakpinar *et al.*, 2005). Moreover, ROS interact with the renal mitochondrial membranes producing large amounts of oxygen radicals that cause deterioration of the kidney architecture (Tabassum *et al.*, 2007). In the current study, treatment with TAM for 14 days caused renal oxidative stress by increasing the Malondialdehyde (MDA) level, as an indicator of lipid peroxidation, and altered non-enzymatic and enzymatic antioxidant systems in the renal tissues through the reduction of GSH, CAT, SOD, GPx and GST activities. In accordance with these obtained data, (El-Beshbishy 2005), reported that administration of TAM caused an elevation in lipid peroxidation which is attributed to the reduction in nicotinamide adenine dinucleotide phosphate (NADPH), which involved in the protecting against ROS inside the cells. In addition, the activities of some intracellular antioxidant enzymes decreased with the increase of lipid peroxidation level (Diplock, Rice-Evans, and

Burdon 1994). GSH is the non-enzymatic antioxidant present in cells that have a vital role in the defense against oxidative stress induced by cell injury. Moreover, it is protecting cells against ROS. The progress of nephrotoxicity may be affected by depleting GSH activity which consequently causes an inhibition of GPx that makes the cells more susceptible to the injury occurred by oxidative stress (Brittebo *et al.*, 1993). SOD is a specific antioxidant enzyme that dismutase  $O_2^-$ , forming  $H_2O_2$ , which is scavenged by CAT or GPx. Both enzymes, CAT, and GPx together convert hydrogen peroxide to water (Fadilloğlu *et al.*, 2003). GST plays a significant role in the detoxification of foreign compounds. The results of the present study demonstrate that TAM treatment causes oxidative tissue damage, as assessed by decreased GSH, CAT, SOD, GPx, GST activities in the kidney. These finding data are in line with the finding of (Tabassum *et al.*, 2007). On the contrary, sodium butyrate treatment improved the enzymatic and non-enzymatic antioxidant enzymes in the renal tissues that protect the kidney against TAM caused nephrotoxicity. Moreover, Tamoxifen-induced mitochondrial NO that stimulates the increases in mitochondrial peroxynitrite, which causes ROS and reactive nitrogen species (RNS) (Nazarewicz *et al.*, 2007). In the current study, the overproduction of ROS and RNS may be related to damage to vasculature or structures of the kidneys which were established by the histopathological examination of renal architecture. Where, the congestion in the glomerular capillary tuft and absence of epithelial cells of the renal tubules were reflected the severe pathological effect of TAM and consequently, altered the kidney function tests and the damage the defense system of the kidney. These data are accordance with (Ahmed *et al.*, 2008) who mentioned that the oral TAM therapy is associated with impairment of kidney function. From all the previous results, this study suggests that the depletion of the redox system and liberation of MDA and free radicals by treatment with TAM caused an alteration in the kidney structure which consequently, affect the kidney function through elevation of the endogenous end products, creatinine, urea and uric acid in the blood. On the other hand, (Padillo *et al.*, 2005) showed that the damage occurred in the kidney by TAM is due to impairment in the liver due to hyperbilirubinemia. Moreover, the increased level of bilirubin caused significant alterations in kidney function and damage to the renal epithelium. The previous study hypothesized that the association between the elevation in bilirubin and kidney dysfunction mainly reflects the link between serum bilirubin concentrations with nonalcoholic fatty liver disease (NAFLD) which induced by TAM therapy in more than 30% of breast cancer patients (Targher *et al.*, 2009). Our previous study (Saleh *et al.*, 2016) showed that the administration of TAM for 14 days caused an elevation in bilirubin level and this level was diminished by the administration of NaBu for 7 consecutive days. On the other hand, kidney function tests were improved in rats treated with TAM and NaBu as compared to the TAM treated group. The results of the current study indicated that the exogenously administered NaBu may reduce TAM-induced nephrotoxicity in rats. The therapeutic effect of NaBu may be attributed to its role to promote liver

lipogenesis and prevent the progression of NAFLD which in turn decreased the bilirubin level and return the kidney function tests nearly to the normal levels (Daubioul *et al.*, 2002; Oldfield IV and Johnson 2015).

## CONCLUSION

The results of the present study revealed that the administration of TAM for 14 days caused oxidative stress mediated damage in the renal tissues. Oxidative stress generated by TAM could increase the levels of kidney function tests, MDA, and NO contents. In addition to the marked depletion in the antioxidant defense resulting nephrotoxicity. These alterations in the defense system affect the structure of the kidney architecture. The exogenously administered sodium butyrate may attenuate TAM-induced renal toxicity in rats. The proposed mechanism of sodium butyrate to improve the function of the kidney probably due to ameliorate the levels of creatinine, urea, and uric acid. Moreover, it could counteract the toxicity action of renal free radicals generated by TAM through the upregulation of oxidant defense system.

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