

RESEARCH ARTICLE

## POTENTIAL MODULATORY EFFECT OF SODIUM BUTYRATE ON TAMOXIFEN CITRATE-INDUCED DAMAGE IN THE SMALL INTESTINE OF RATS

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### ABSTRACT

Tamoxifen was approved for breast cancer chemoprevention in high-risk women despite its side effects, especially on gastrointestinal tract. Therefore, this study aimed to demonstrate the therapeutic and protective properties of sodium butyrate (SB; 300 mg/kg body weight) against the small intestine injury induced by tamoxifen citrate (TC; 40 mg/kg body weight) in rats. Forty-nine male Wistar rats were randomly allotted into 5 main groups: the control group (where the rats received oral saline), SB group, TC group, SB-TC group (where SB was given before TC), and TC-SB group (where TC was given before SB). SB in TC-SB group increased the regenerative capacity of damaged intestinal tissue, decreased significantly ( $P<0.05$ ) the level of intestinal malondialdehyde, and increased significantly ( $P<0.05$ ) the reduced glutathione level and the activities of glutathione peroxidase, catalase, and superoxide dismutase in the intestinal tissues compared with the TC-treated group. SB also suppressed the proinflammatory cytokine response and reduced oxidative DNA damage in the intestinal tissues of the TC-SB group compared with the TC-treated group. In conclusion, this study suggested that SB reduced the harmful effects of TC on the intestinal tissues of the rats by reducing oxidative stress and decreasing the generation of proinflammatory cytokines.

### Article History:

Received: 6 February 2022  
Revised: 24 February 2022  
Accepted: 24 February 2022

Published Online:  
4 March 2022

### Keywords:

Comet assay  
Oxidative stress  
Small intestine  
Sodium butyrate  
Tamoxifen

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### INTRODUCTION

Breast cancer is the most common invasive cancer among women; estrogen receptors (ERs) are expressed in 75% of breast cancers<sup>[1]</sup>. Tamoxifen inhibits the growth of ER-negative cell lines at low concentrations and also inhibits the growth of other non-ER cell types<sup>[2]</sup>. Tamoxifen, an anti-estrogenic and non-steroidal drug, is widely used in clinics for hormonal and adjuvant therapy in early and advanced metastatic breast cancer in post-menopausal women. This drug is approved for breast

cancer chemoprevention in high-risk women<sup>[3]</sup>. It is a lipophilic drug, slightly soluble in water; the saline form of tamoxifen citrate (TC) is usually used to improve its solubility in aqueous media<sup>[3]</sup>. Tamoxifen has a powerful anti-tumor effect on both pre and postmenopausal women as it struggles to occupy intracellular estrogen receptor sites in the target tissue and thus blocks the action of biologically active estrogens<sup>[4]</sup>. However, long-term treatment with TC causes vomiting, nausea, abdominal cramps, pulmonary embolism, ocular

problems, venous thrombosis, thromboembolic disorders, and endometrial cancer<sup>[5]</sup>. Furthermore, 30–40% of women with estrogen receptor-positive breast cancer will develop metastases and die even with TC treatment<sup>[6]</sup>. It has been shown that TC is associated with higher oxidative DNA damage, lipid peroxidation damage, and upregulation of certain antioxidant enzymes in rat bone marrow cells<sup>[7]</sup>. An imbalance between the production of active oxygen species (ROS) and the rate at which they are eliminated by antioxidants leads to oxidative stress, which damages intracellular lipids, proteins, and mitochondrial DNA and may also damage cell structure and function<sup>[8]</sup>. Thus, it is necessary to develop a combination therapy to reduce these side effects of tamoxifen and improve bioavailability when it is taken orally.

The addition of antioxidant supplementation with cancer chemotherapy may cause a significant reduction in toxicity<sup>[9]</sup>. The antioxidant and anti-inflammatory efficacy of butyrate has attracted attention in recent years. The active component of butyrate is butyric acid, an important short-chain fatty acid, produced by the fermentation of intestinal microbiota, which is present in the gastrointestinal tract<sup>[7,10]</sup>. Butyrate is the main energy source for the intestinal epithelium, it maintains the homeostasis of the gut<sup>[11]</sup>, and therefore has the effect of improving the morphology of the gastrointestinal tract and also has an important role in maintaining the balance of the intestinal microflora that plays an important physiological role in maintaining the health and integrity of the colon mucosa<sup>[12]</sup>.

Sodium butyrate (SB), a white powdery substance with a strong rancid cheese-like odor is often used in place of butyric acid itself, because it is solid and stable. SB acts as an important acidifier to reduce gastric emptying, improve feed digestibility, and stimulate growth and differentiation of the gastrointestinal mucosa of piglets<sup>[13]</sup>. Moreover, SB is a potent histone deacetylase inhibitor inhibiting the expression

of inflammatory mediators in diverse diseases<sup>[14]</sup>. Other studies proved that butyrate or its salt enhances wound healing in intestinal surgery, alleviates intestinal inflammation<sup>[15]</sup>, and inhibits the growth of various cancer cells<sup>[16]</sup>. SB can also protect a human liver cancer cell line against oxidative stress by modulating the activity of antioxidant enzymes, inhibiting the ROS and malondialdehyde (MDA) levels, and able to decrease the oxidative DNA damage through up-regulation of the reduced glutathione (GSH), glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD), and exerts its antioxidant effect by regulating the PI3K/AKT pathway, and nuclear factor erythroid 2-related factor (Nrf2)<sup>[17]</sup>. It was also reported that butyrate can act as an immunomodulator that suppresses the production of proinflammatory mediators by immune cells [such as interferon (IFN)- $\gamma$ , tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1 $\beta$ , IL-8, and IL-6] and hence reducing the inflammatory reaction<sup>[18]</sup>. Moreover, SB improved spatial learning and memory ability in mice model of neurodegenerative diseases<sup>[19]</sup>, as well as attenuated acute lung injury induced by severe burn<sup>[20]</sup>, and acute liver failure induced by toxins in rats<sup>[21]</sup>. Therefore, the purpose of this work is to utilize some properties of SB as an anticancer, anti-inflammatory, and antioxidant agent to reduce the effect of tamoxifen-induced intestinal damage in rats as a promising therapy when administered together.

## MATERIAL AND METHODS

### Chemicals and reagents

TC tablets (containing 20 mg TC) were purchased from (AstraZeneca, Cairo, Egypt). The SB pure powder used in this study was purchased from Sigma Aldrich (St. Louis, MO, USA).

### Animals

Forty-nine adult male Wistar rats weighing 230–250 g, aged 3–4 months were purchased from the National Research Center (NRC,

Giza, Egypt). The rats were randomly assigned to stainless steel cages (7 rats/cage) and acclimatized for seven days before the experiments in standard conditions of humidity  $51\pm0.5\%$ , and temperature  $23\pm3^{\circ}\text{C}$  with light/dark cycle (12/12 hours), and access *ad libitum* to fresh tap water and standard rodent diet.

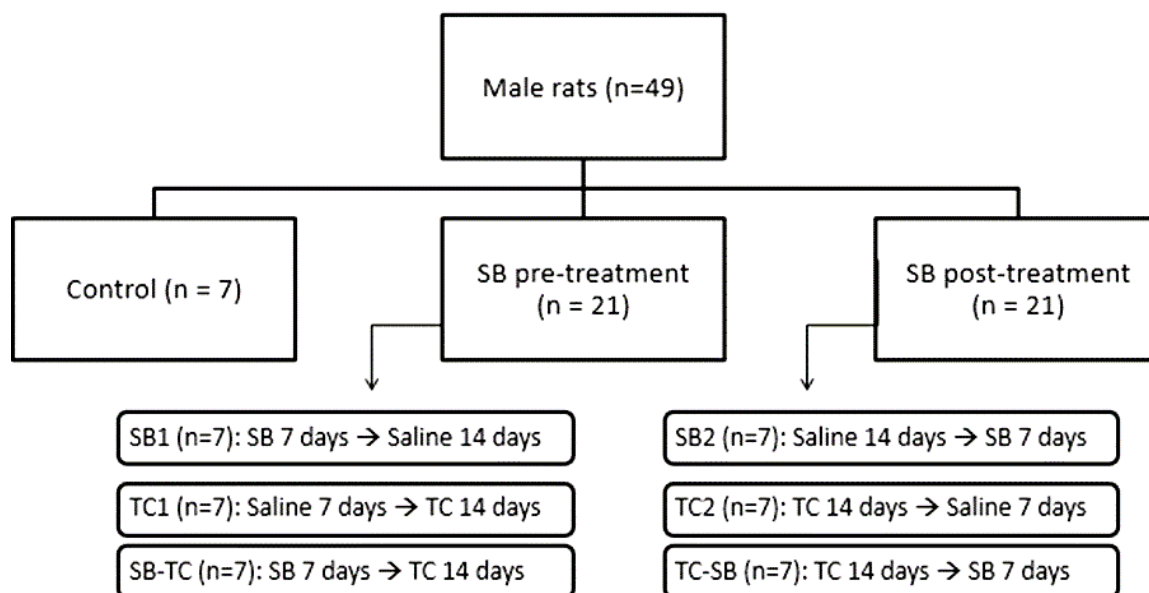
### Ethical considerations

The protocol for animal care and handling used in this study was approved by the Institutional Animal Care and Use Committee (IACUC), Faculty of Science, Cairo University, Giza, Egypt (CUFS/F/

PHY/45/15). No pathological symptoms were observed during the experimental periods.

### Experimental design

Forty-nine male rats were randomly allotted into three main groups as shown in Figure "1". TC (40 mg/kg) and SB (300 mg/kg) were dissolved in saline and were administrated orally. The dose of SB has been reported to reduce the MDA level and inhibit the expression of TNF- $\alpha$  gene. The doses of TC and SB were chosen from previously published reports<sup>[22,23]</sup>.



**Figure 1:** Classification of main groups: 1- Control group (n=7), rats received saline orally for 21 days. 2- SB pre-treatment group (n=21), rats were divided into three subgroups (7 rats/group): subgroup SB1, rats received SB for 7 days and then received saline for 14 days, subgroup TC1, rats received saline for 7 days and then TC for 14 days, and subgroup SB-TC, rats received SB for 7 days and then TC for 14 days. 3- SB post-treatment group (n=21): rats were divided into three subgroups (7 rats/ group): subgroup SB2, rats received saline for 14 days and then received SB for 7 days, subgroup TC2, rats received TC for 14 days and then received saline for 7 days, and subgroup TC-SB, rats received TC for 14 days and then received SB for 7 days.

### Sample's processing

By the end of the experiment, rats were fasted overnight then euthanized under chloroform vapor and sacrificed. Sections of the small intestine from all the experimental groups were collected, weighed, and washed

with isotonic saline solution and then divided into four parts. The first part was fixed in 10% buffered formal saline for the histological study. The second part was immediately frozen in liquid nitrogen and stored under  $-80^{\circ}\text{C}$  until used for enzyme-

linked immunosorbent assay (ELISA). The third part was homogenized in ice-cold Tris-HCl buffer (pH=7.4). The homogenates were centrifuged at 2000 ×g for 15 minutes at 4°C, and the resultant supernatant was stored immediately at -80°C until used for the antioxidant markers detection. The last part was mixed with mincing buffer and stored at -80°C for the comet assay.

### **Intestinal histology**

Preserved tissue segments were washed, dehydrated by ethanol, cleared in xylene, and embedded in paraffin according to the standard histological procedures. The segments were cut in 4 µm thickness and stained with hematoxylin and eosin and examined by a light microscope (Leica Microsystems, Wetzlar, Germany). All histopathological processing and assessment of specimens were performed by two independent observers blinded to the experimental protocol.

### **Measurement of malondialdehyde (MDA) level**

MDA level, a marker of oxidative stress and a key indicator for lipid peroxidation, was measured in small intestine tissue samples according to the thiobarbituric acid (TBA) assay by Ohkawa *et al.*<sup>[24]</sup>. TBA reacts with MDA in an acidic medium to form the thiobarbituric acid reactive product with a resultant color, the absorbance of the resulting pink product was measured using a spectrophotometer with a wavelength of 535 nm, and the results were expressed as nmol/g tissue.

### **Determination of reduced glutathione (GSH) level and the activity of antioxidant enzymes**

GSH level in the intestine sample was determined following Beutler *et al.*<sup>[25]</sup>. GPx, CAT, and SOD activities were measured according to the methods of Paglia and valentine<sup>[26]</sup>, Aebi<sup>[27]</sup>, Nishikimi *et al.*<sup>[28]</sup>, respectively using Bio-diagnostic assay kits (Biodiagnostic Company for Diagnostic and Research Reagents, Giza,

Egypt) according to the manufacturer's instructions.

### **Evaluation of the proinflammatory cytokines**

The concentrations of rat IL-1β and TNF-α were measured in the small intestine tissues using ELISA kits (CSB-E08055r and CSB-E11987r, respectively, Koma Biotech Inc., Seoul, Korea) following the manufacturer's instructions. The optical density was read at a wavelength of 450 nm using an ELISA reader (DAS Company, Rome, Italy) and was expressed as pg/g tissue.

### **Detection of DNA damage (comet assay)**

Alkaline comet assay analysis was performed by using Tice *et al.*<sup>[29]</sup> method to determine the intestinal DNA damage of treated and non-treated groups. Images of isolated comets were randomly selected and were analyzed by using (Comet Assay IV software, Perceptive Instruments, Suffolk, UK). Tail length, percentage of DNA in the tail, and the tail moment were used as evaluation of the DNA damage.

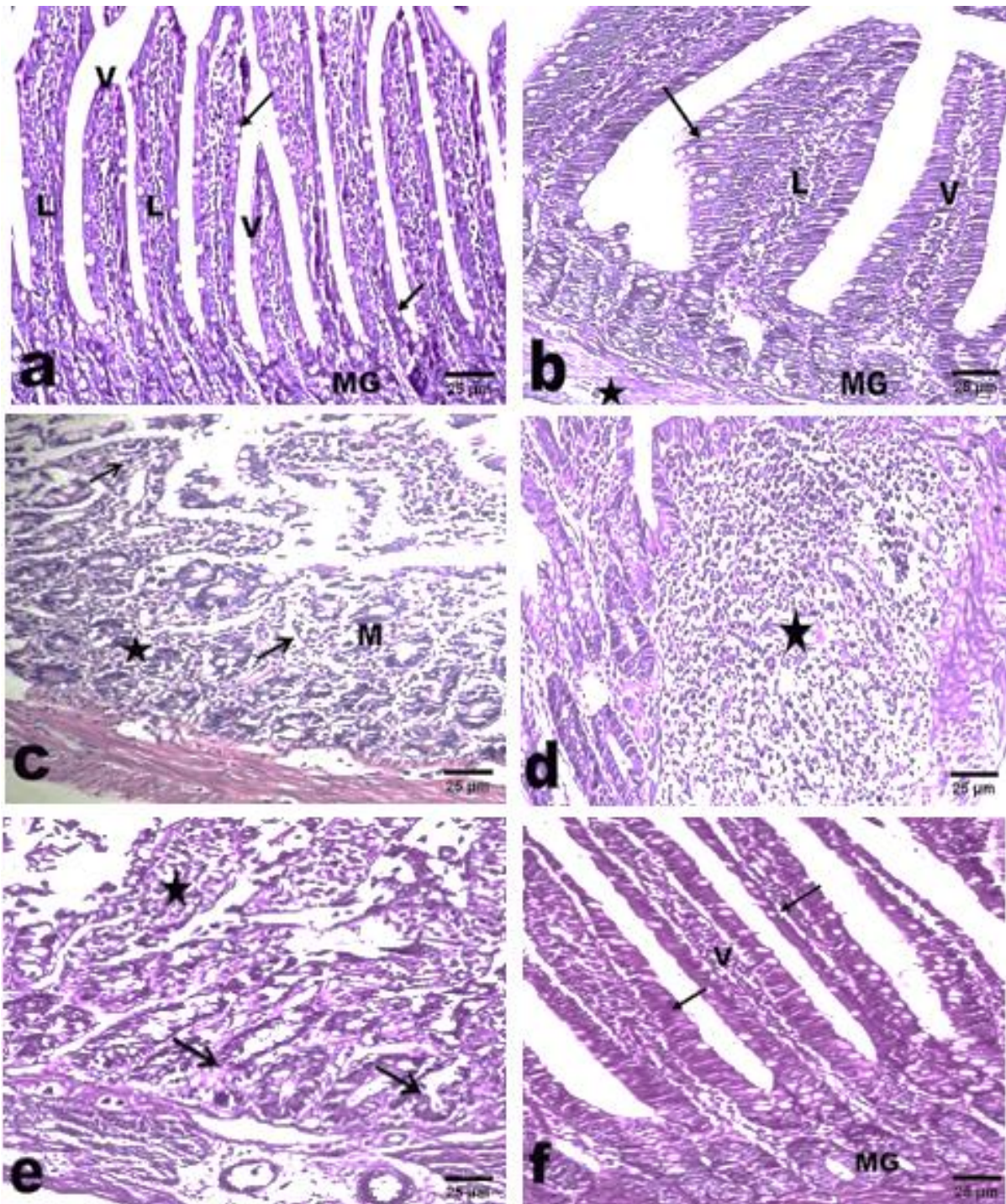
### **Statistical analysis**

All results were expressed as means ± standard deviation for each group. Data were analyzed by GraphPad Prism 5.0 software (GraphPad Software, Inc., San Diego, CA, USA). The differences among the experimental groups were detected by one-way ANOVA, followed by a post-hoc Bonferroni test. Values of *P*<0.05 were regarded statistically significant.

## **RESULTS**

### **The modulatory effect of sodium butyrate against tamoxifen citrate-induced histological alteration in the small intestine**

The comparison between the different groups was histologically distinguished in Figure "2" that is affirmed thereafter by the biochemical evaluation. In the SB group, no destructive changes were observed; Figure "2b" showed healthy intestinal mucosa and submucosa. The most severe damage to the intestinal tissue was observed in the TC group that was characterized by loss of villi

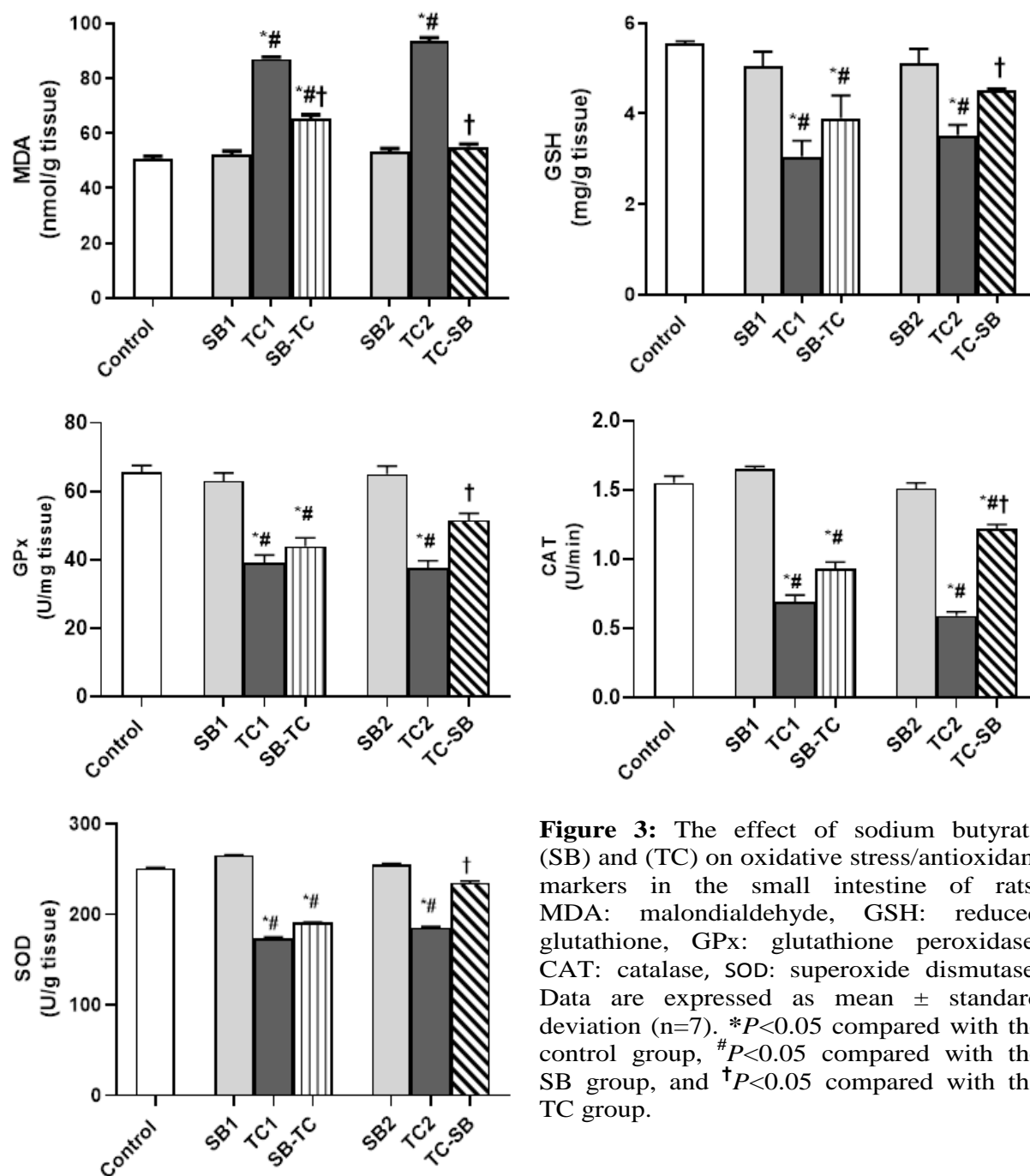


**Figure 2:** Photomicrographs of sections of rat's small intestine stained with hematoxylin and eosin. **(a)** Control group showing intact mucosa and submucosa, normal villi (V), enterocytes (arrows), lamina propria (L), and mucous glands (MG);  $\times 100$ . **(b)** Sodium butyrate (SB) group showing normal intestinal layers, normal villi (V), enterocytes (arrow), lamina propria (L), mucous glands (MG), normal submucosa (\*);  $\times 100$ . **(c)** Tamoxifen citrate (TC) group showing loss of villous integrity, mucosal necrosis (\*) in mucosal layer (M), and heavy infiltration of inflammatory cells (arrows);  $\times 200$ . **(d)** TC group showing hyperplasia in submucosa (\*);  $\times 100$ . **(e)** SB-TC group showing the deteriorating layers of the intestine, the degeneration of the intestinal glands (arrows), the degenerated villi (\*) with desquamated epithelium;  $\times 200$ . **(f)** TC-SB group showing the regenerated villi (V) with normal enterocytes (arrows) and healthy intestinal mucous glands (MG);  $\times 200$ .

integrity, focal necrosis of the mucosa, and heavy inflammatory cells infiltration (Figure 2c,d). Oral SB supplementation for 7 days and then TC for 14 days in the SB-TC group showed deterioration of intestinal layers, degeneration of villi, and mucous glands (Figure 2e). The TC-SB group (Figure 2f) showed less infiltration of inflammatory cells and attenuation of villus, and intact intestinal mucous glands. Thus, TC-induced histological changes in the small intestine were effectively mitigated by SB treatment.

### The modulatory effect of sodium butyrate against tamoxifen citrate-induced oxidative stress in the small intestine

Intestinal MDA concentration was used to assess the intestine oxidative stress. In rats received TC, the MDA level was increased significantly ( $P < 0.05$ ) compared with the control group and SB group. In SB-TC and TC-SB groups, the MDA level decreased significantly ( $P < 0.05$ ) compared with the TC group as shown in Figure “3”. Oral administration of TC showed a marked



**Figure 3:** The effect of sodium butyrate (SB) and (TC) on oxidative stress/antioxidant markers in the small intestine of rats. MDA: malondialdehyde, GSH: reduced glutathione, GPx: glutathione peroxidase, CAT: catalase, SOD: superoxide dismutase. Data are expressed as mean  $\pm$  standard deviation (n=7). \* $P < 0.05$  compared with the control group, # $P < 0.05$  compared with the SB group, and † $P < 0.05$  compared with the TC group.

decrease in the level of GSH and the activities of GPx, CAT, and SOD compared with the control group and the SB group (Figure 3). On the other hand, SB administration caused a non-significant increase in the activities of antioxidant biomarker enzymes in the small intestine of rats in the SB pre-treatment group compared with the TC group as shown in Figure "3". A significant increase ( $P < 0.05$ ) in the level of GSH, and the activities of GPx, CAT, and SOD were shown in the TC-SB group compared with the TC group.

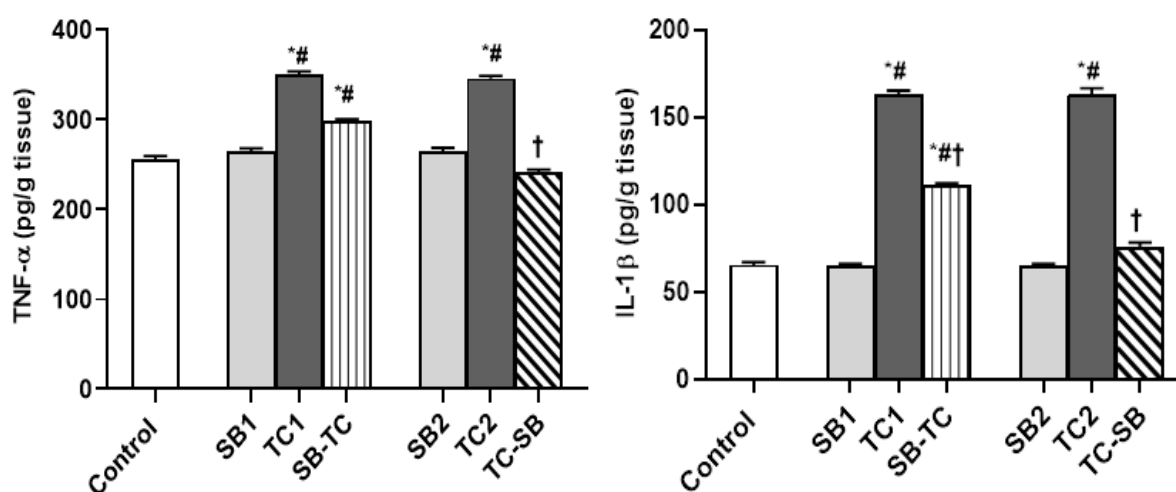
#### The modulatory effect of sodium butyrate against tamoxifen citrate-enhanced the proinflammatory cytokine production in the small intestine

Elevated levels of TNF- $\alpha$  and IL-1 $\beta$  were found in the TC group compared with the control group ( $P < 0.05$ , Figure 4). SB administration in the pre-treatment group reduced significantly ( $P < 0.05$ ) the levels of

IL-1 $\beta$  relative to that found in TC group. Whereas, the SB in the post-treatment group induced a significant decrease ( $P < 0.05$ ) in the level of TNF- $\alpha$  and IL-1 $\beta$  as compared with the TC group (Figure 4).

#### The modulatory effect of sodium butyrate against tamoxifen citrate-induced DNA fragmentation in the small intestine

Figure "5" showed the DNA damage in the comet assay induced by TC compared with the undamaged DNA in the control group. All DNA fragmentation parameters (tail length, tail intensity, and tail moment) in the TC-treated group were significantly higher ( $P < 0.05$ ) compared with the control group and the SB group indicating a significant DNA damage (Figure 6). The SB-TC group and TC-SB group showed a significant decrease ( $P < 0.05$ ) in all DNA fragmentation parameters compared with the TC group demonstrating the protective and therapeutic effect of SB on DNA damage.

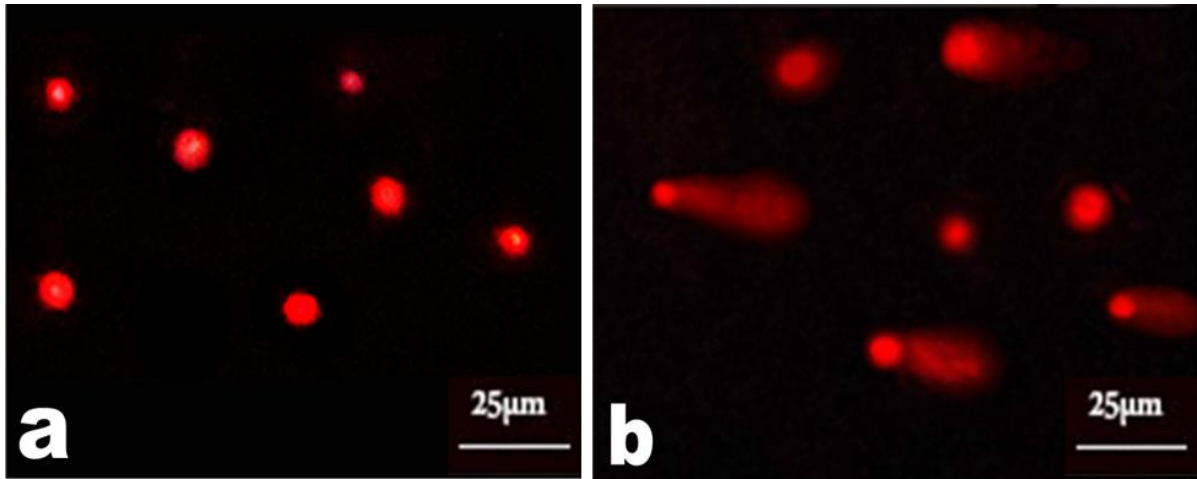


**Figure 4:** The effect of sodium butyrate (SB) and (TC) on the concentration of proinflammatory cytokines in the small intestine of rats. TNF- $\alpha$ : tumor necrosis factor, IL: interleukin. Data are expressed as mean  $\pm$  standard deviation (n=7). \* $P < 0.05$  compared with the control group, # $P < 0.05$  compared with the SB group, and  $\dagger P < 0.05$  compared with the TC group.

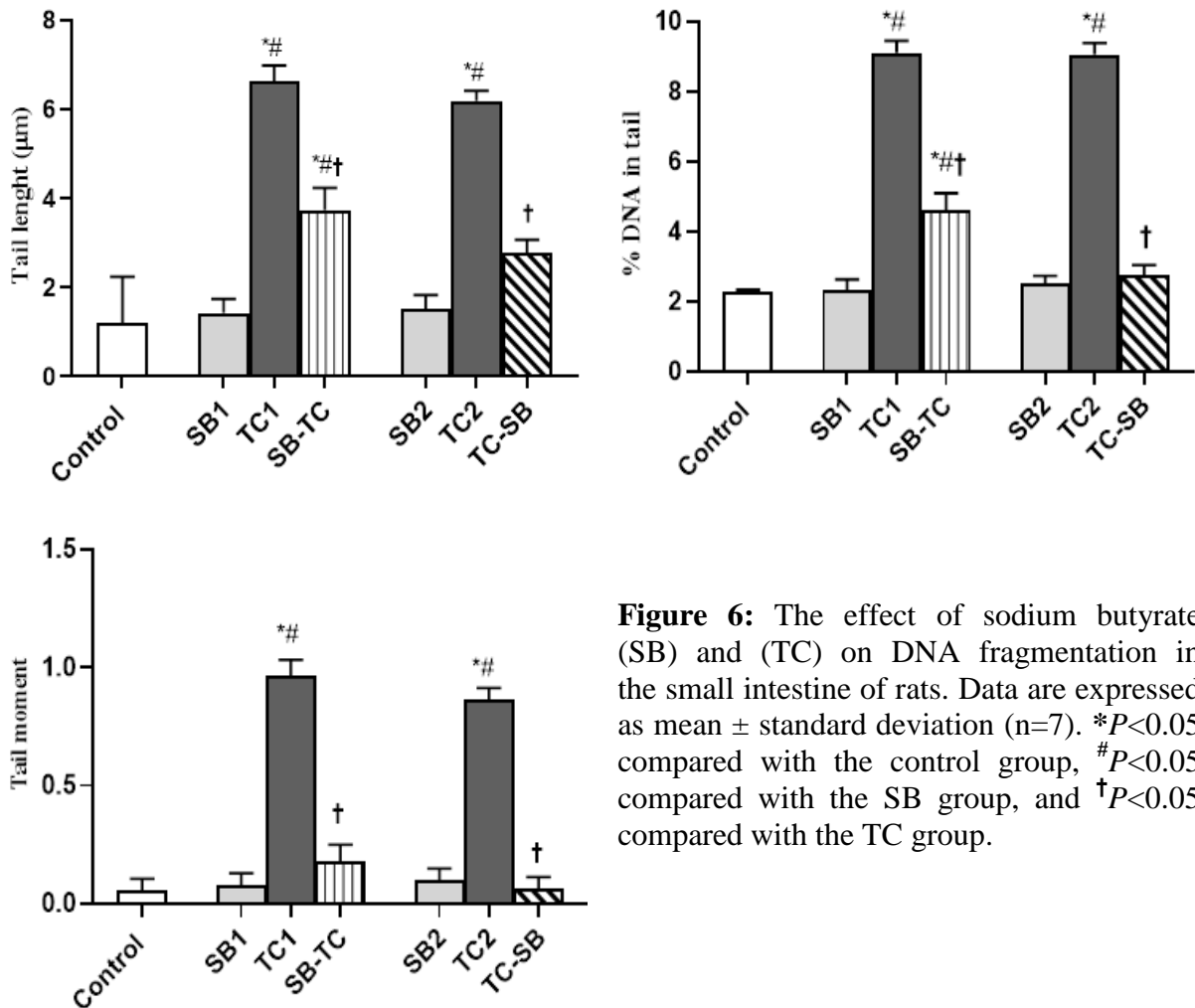
#### DISCUSSION

The current study revealed the attenuating effects of SB on the small intestine injury of rats receiving TC. It alleviated the histological changes in the small intestine,

increased the level of GSH and the activities of GPx, CAT, and SOD in the intestinal tissue, and reduced the intestinal MDA, TNF- $\alpha$ , and IL-1 $\beta$  levels, as well as DNA damage induced by TC administration.



**Figure 5:** Photos of comet assay showing (a) undamaged DNA in the control group compared with (b) damaged DNA induced by TC in the small intestine of rats.



**Figure 6:** The effect of sodium butyrate (SB) and (TC) on DNA fragmentation in the small intestine of rats. Data are expressed as mean  $\pm$  standard deviation (n=7). \* $P$ <0.05 compared with the control group, # $P$ <0.05 compared with the SB group, and † $P$ <0.05 compared with the TC group.

TC induces the regression of the tumor in women with advanced metastatic breast cancer by blocking the action of active

estrogen and estradiol in the target tissue<sup>[4]</sup>. Another antitumor mechanism of TC is to inhibit cell proliferation by arresting



the cell cycle leading to apoptosis of breast cancer cells<sup>[30]</sup>. In this study, TC was delivered orally, which is the most preferred administration route as previously described<sup>[31,32]</sup>. The histological changes seen in the current study after TC administration including loss of villi integrity, focal necrosis of the mucosa, and heavy inflammatory cells infiltration can be attributed to its heavy metabolism during the penetration through the intestinal mucosa of the rat<sup>[33]</sup>. Moreover, TC decreases the fluidity of the cell membrane of breast cancer cells<sup>[34]</sup> and may trigger transmembrane signal transduction and oxidative stress.

Concerning oxidative stress, this study confirms that TC increases the production of ROS causing lipid peroxidation, which may cause damage to the cell function and structure. The increment in MDA level in the small intestine of rats that received TC was also demonstrated by El-Shorbagy<sup>[7]</sup> who showed the same results in rat bone marrow cells. Consequently, the increase of lipid peroxidation reduces some intracellular antioxidant enzymes. Oral administration of TC was accompanied by decreasing in the GSH level and the activities of GPx, CAT, and SOD in intestinal tissues (as found in the current study), bone marrow cells<sup>[7]</sup>, and liver tissues<sup>[35]</sup>. The depletion of GSH increases oxidative stress, while SOD and CAT act as antioxidant enzymes, which protect against ROS<sup>[36]</sup>. In the current study, the increase in MDA production and the reduction of antioxidant mediators GSH, GPx, CAT, and SOD could be responsible for the pathophysiology of TC damage. All the above features were accompanied by an elevated level of TNF- $\alpha$  and IL-1 $\beta$  in the TC group, which accelerated the inflammatory reactions. These findings align with previous reports that showed that treatment of rats with TC increased hepatic TNF- $\alpha$  level compared with the control group<sup>[37,38]</sup>.

A major aspect that has been associated with the carcinogenicity of TC is that its metabolites bind covalently to DNA,

resulting in the formation of DNA adducts<sup>[39]</sup>. *In vitro* study has revealed that the formation of DNA adducts by TC were thought to be mediated through the generation of free radical species and chromosomal breaks<sup>[39]</sup>. The present study indicated that all DNA fragmentation parameters (tail length, tail intensity, and tail moment) in the TC-treated group were significantly higher than the control group, which means that TC caused significant DNA damage in rats. The DNA damage induced by TC was detected in all species and strains of laboratory animals in which it has been studied<sup>[7,35,40]</sup>. As such, combination therapy is necessary as the main strategy to increase response and reduce resistance in cancer therapy; furthermore, the addition of antioxidants with cancer chemotherapy (tamoxifen) may reduce toxicity upon chronic administration.

SB is a salt composed of a short-chain fatty acid with four carbons, it plays an important role in inhibiting intestinal pathogenic bacteria, modulating immunity, and regulating the intestinal barrier<sup>[18]</sup>. The current study demonstrated the effect of SB in combination with TC as a protective or therapeutic agent to mitigate TC-induced genotoxicity and intestinal injury. In addition, SB did not induce any toxicity since no changes were observed in the structure of the small intestine and the level of the antioxidant enzyme, as well as no DNA damage was observed in the small intestine of rats after oral administration of SB compared with the control group. Pospelova *et al.*<sup>[41]</sup> used the comet assay to show that there are no obvious DNA breaks in the senescent cells caused by SB. Furthermore, the results of Rosignoli *et al.*<sup>[42]</sup> showed no DNA damage after incubating colon cells and cancer cell lines with butyrate in presence of the oxidative agent "H<sub>2</sub>O<sub>2</sub>".

In the present study, it was found that TC-SB group showed the best results compared with the TC and SB-TC groups. Consistently butyrate in the TC-SB treatment group was able to reduce

inflammatory cells infiltration, attenuate villi formation and improve intestinal mucosal gland damage induced by TC administration. Other researchers have reported the role of SB not only in providing energy to intestinal epithelial cells, but also in promoting epithelial cell growth, differentiation, and proliferation<sup>[12]</sup>, increasing the length of the intestinal villi, and enlarging the absorptive surface of the gut<sup>[43]</sup>.

The mechanisms of SB in improving the morphology and structure of the intestinal mucosa were associated with the inhibition of cell apoptosis by promoting the expression of anti-apoptotic factor, regulating gene expression, and regulating protein synthesis<sup>[44]</sup>. Moreover Wu *et al.*<sup>[45]</sup> showed that SB attenuated macrophage activation, reduced inflammatory factor production, restored gut tight junction proteins, and maintained the intestinal mucosal integrity. The thickening of the intestinal mucosa in piglets is attributed to the antibacterial and anti-inflammatory effect of sodium butyrate<sup>[13]</sup>.

In the current study, the intestinal MDA level increased after TC administration and was significantly reduced by SB treatment in TC-SB group. The present study demonstrated significant improvements in the antioxidant mediators (GSH, GPx, CAT, and SOD) in the small intestine of rats upon treatment with SB. These data suggested that SB administration effectively augmented the antioxidant defense system of the intestine. These results are consistent with Liu *et al.*<sup>[46]</sup> who showed that SB improves antioxidant function in dairy calves before weaning.

In addition, the level of TNF- $\alpha$  and IL-1 $\beta$  was significantly decreased in the TC-SB group relative to the control group, indicating the ability of SB to attenuate the inflammatory response and maintain the cytokine balance at normal levels. Previous studies also revealed that SB reduced inflammation and mucosal lesion in experimental acute ulcerative colitis, cecal ligation, and puncture-induced

sepsis<sup>[18,47]</sup>. In addition, it decreased the expression of cytokines (such as IL-6, IL-10, IFN- $\gamma$ , and IL-1 $\beta$ ) and modulated B and T cells function in chicken, which may be one of the immune-enhancing mechanisms of SB<sup>[48]</sup>.

On the other hand, SB decreased significantly the DNA fragmentation induced by TC in the current study. Hamer *et al.*<sup>[49]</sup> demonstrated that butyrate acts as a secondary antioxidant by affecting the oxidative stress and enhancing DNA repair in the human colonic mucosa. It also showed a protective effect against DNA damage caused by H<sub>2</sub>O<sub>2</sub> in human colonocytes<sup>[42]</sup>.

In conclusion, the current study demonstrated that the deleterious effects of TC given in the SB-TC group were overwhelmed the protective ability of SB in the repair mechanism. Thus, oral administration of SB as a therapeutic agent is more effective than using it as a protective agent against TC-induced damage in the small intestine of rats. The current study suggested the use of SB, as a promising agent, in reducing TC-induced genotoxicity that may improve the health of breast cancer patients without noticeable drawbacks. However, further preclinical and clinical studies are needed to further prove the molecular mechanisms of the beneficial effects of SB against the toxicity of TC and other chemotherapeutic agents.

#### **FUNDING SOURCE DISCLOSURE**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

#### **CONFLICT OF INTEREST**

Author declares that there is no conflict of interest in this study.

#### **ACKNOWLEDGEMENTS**

The author expresses full gratitude to Dr. Hanan Ebead Saleh (Associate Professor of Physiology, Zoology Department, Faculty of Science, Cairo University) for her valuable cooperation in the statistical analysis review.

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**How to cite this article:**

Hussein, R. M. (2022). Potential modulatory effect of sodium butyrate on tamoxifen citrate-induced damage in the small intestine of rats. *Egyptian Journal of Zoology*, 77: 53-66 (DOI: 10.21608/ejz.2022.114806.1069).

## التأثير المحتمل لبوتيرات الصوديوم في تخفيف الضرر الناجم عن عقار سترات التاموكسيفين في الأمعاء الدقيقة للجردان

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تمت الموافقة على عقار تاموكسيفين كعلاج كيميائي لسرطان الثدي لدى النساء المعرضات للمخاطر العالية على الرغم من تأثيراته الجانبية وخاصة على الجهاز الهضمي. تهدف الدراسة الحالية إلى إظهار الخصائص العلاجية والوقائية لبوتيرات الصوديوم (300 مجم/كجم من وزن الجسم) ضد إصابات الأمعاء الدقيقة التي يسببها عقار سترات التاموكسيفين (40 مجم/كجم من وزن الجسم) في الجردان. تم توزيع تسعة وأربعين جرد ذكر من سلالة "Wistar" بشكل عشوائي إلى 5 مجموعات رئيسية: المجموعة الضابطة (حيث تلقت الجردان محلول ملحي عن طريق الفم)، ومجموعة بوتيرات الصوديوم، ومجموعة سترات التاموكسيفين، ومجموعة بوتيرات الصوديوم-سترات التاموكسيفين (حيث تم إعطاء بوتيرات الصوديوم قبل سترات التاموكسيفين)، ومجموعة سترات التاموكسيفين-بوتيرات الصوديوم (حيث تم إعطاء سترات التاموكسيفين قبل بوتيرات الصوديوم). وقد وجد أن بوتيرات الصوديوم في مجموعة سترات التاموكسيفين-بوتيرات الصوديوم زادت من القدرة التجديدية للأنسجة المعوية التالفة، وخفضت بشكل ملحوظ إحصائياً ( $P < 0.05$ ) من مستوى نواتج فوق أكسدة الليبيدات المعوية. كما زادت من مستوى الجلوتاثيون المختزل بشكل ملحوظ إحصائياً ( $P < 0.05$ ) ونشاطات الجلوتاثيون بيروكسيداز، والكاتالاز، وفوق أكسيد الديسموتاز في أنسجة الأمعاء مقارنة بالمجموعة المعاملة بسترات التاموكسيفين فقط. كما خفضت أيضاً بوتيرات الصوديوم استجابة السيتوكينات المنشطة للالتهاب وتلف الحمض النووي الناتج عن الأكسدة الخلوية في مجموعة سترات التاموكسيفين-بوتيرات الصوديوم مقارنة بالمجموعة المعاملة بسترات التاموكسيفين فقط. وخلصت الدراسة الحالية إلى أن استخدام بوتيرات الصوديوم قلل من التأثيرات الضارة لسترات التاموكسيفين على الأنسجة المعوية للجردان عن طريق تقليل الإجهاد التأكسدي والحد من توليد السيتوكينات المسببة للالتهابات.