2022, Scienceline Publication
World's Veterinary Journal
World Vet J, 12(3): 323-329, September 25, 2022
ISSN 2322-4568
DOI: https://dx.doi.org/10.54203/scil.2022.wvj41

Amelioration of Hepatotoxicity by Sodium Butyrate Administration in Rats

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ORIGINAL ARTICLE
pii: S232245682200041-12
Received: 26 July 2022
Accepted: 11 September 2022

ABSTRACT

Lead poisoning is a serious environmental issue with life-threatening consequences. Lead poisoning increases the risk of cancers, gastrointestinal disorders, hepatotoxicity, central nervous system diseases, nephropathy, and cardiovascular diseases in animals and humans. The current study aimed to investigate the effect of sodium butyrate, as an antioxidant, on protecting female adult rats from the harmful effects of lead acetate. A total of 40 adult female albino rats were divided randomly into four equal groups. The first group dealt as the control. The second group received lead acetate at a dose of 200 mg/kg daily orally. The third group received lead acetate at a dose of 50 mg/kg daily orally, and the fourth group received both sodium butyrate and lead acetate orally/day for 35 days. The result indicated that sodium butyrate reduced the concentration of liver enzymes (ALT, AST, and ALP) which were elevated by lead acetate poising. Moreover, sodium butyrate ameliorates the redux status by decreasing malondialdehyde and increasing total antioxidant capacity. Additionally, sodium butyrate-treated rats showed significant alterations in the expression of peroxisome proliferator-activated receptor gamma and interleukin -10 genes. In conclusion, this study reveals an unrecognized role for peroxisome proliferator-activated receptor gamma and Interleukin-10 signaling after sodium butyrate treatment in regulating the immunopathology that occurs during lead acetate poising.

Keywords: Interleukin-10, Lead acetate toxicity, Sodium butyrate, PPAR-gamma, Rat

INTRODUCTION

Environmental pollutants from industry, such as lead, are widespread. The earth's crust contains a significant amount of pollutants, which can be easily dispersed in the environment. A major environmental disease with potentially fatal effects is lead poisoning. Lead poisoning has been linked to various cancers, gastrointestinal tissues, and cardiovascular diseases in humans and animals, as well as hepatotoxicity, nephrotoxicity, and changes to the central nervous system (Yousef et al., 2019).

Lead can cause oxidative stress, which can cause liver damage, by increasing the generation of free radicals to a certain level and reducing the effectiveness of the antitoxin system (Widiarko and Permata 2020). Butyric acid is a naturally occurring short-chain volatile fatty acid that is employed in the chemical, culinary, pharmaceutical, and animal feed sectors (Brändle et al., 2016). Research has concentrated on strain generation using metabolic engineering and process development employing inexpensive biomass feedstocks for the fermentation-based manufacture of bio-based butyric acid (Zigova and Šturdík, 2000). Butyric acid can potentially reduce harmful intestinal microorganisms while increasing digestibility coefficients. As a result of an increase in the small intestine's absorptive surface and the formation of beneficial bacteria in the gastrointestinal tract, sodium butyrate supplementation can boost feed intake and weight gain (Sikandar et al., 2017). In this regard, sodium butyrate has gained particular attention due to its capacity to suppress mucosal apoptosis via antioxidative, antibacterial, anti-inflammatory, and immunomodulatory effects (Zhang et al., 2015).

Peroxisome proliferator-activated receptor-gamma (PPAR-g) has pleiotropic effects on lipid metabolism, inflammation, and cell proliferation (Ferreira et al., 2014). Since PPAR-g ligands are known to have anti-inflammatory properties, both natural and synthetic versions of them have been tested in experimental models of sepsis. Treatment with Thiazolidinediones and natural PPAR-g ligands can decrease the release of interleukin-6 and interleukin-10 (IL-10), tumor necrotic factors-α, and Chemokine (C-C motif) ligand 2, as well as neutrophil infiltration in the liver and lung brought on by polymicrobial sepsis or endotoxemia (Chima et al., 2008; Han et al., 2017). The PPAR-g agonists also lessen high Mobility Group Box 1 (HMGB1) levels and indicators for organ failure in endotoxemic mice. As a result, the treatments dramatically boost the survival of mice (Collin et al., 2004; Kaplan et al., 2005; Lee et al., 2012).

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It is not yet clear how PPAR-g agonists reduce inflammation. According to a widely recognized theory, active PPAR-g directly interacts with a transcription factor and causes transrepression (Schmidt et al., 2010; Wu et al., 2020). Hemorrhagic shock-induced IkappaB kinase-related kinases activity and IkappaB kinase degradation are decreased by the synthetic PPAR-g agonist pioglitazone (Chima et al., 2008).

The pleiotropic cytokine IL-10, commonly referred to as cytokine synthesis inhibitory factor, plays a crucial role in immunoregulatory processes (Verma et al., 2016). It contains anti-inflammatory qualities and affects the function of several immune system cell types. The main sources of IL-10 secretion include activated T cells, monocytes, macrophages, dendritic cells, natural killer cells, and B cells (Blanco et al., 2008). Excessive IL-10 expression encourages the growth of some lymphomas and melanomas by stifling the antitumor immune response (Huang et al. 1999; Saraiva et al., 2020). The serum level of IL-10 may also signal illness progression. According to a study on individuals with radically resected solid tumors, IL-10 serum levels recover to normal; however, the IL-10 level was found to be continuously high in cases of tumor recurrence (de Vita et al. 2000). The survival and persistence of intracellular infections *in vivo* are fundamentally influenced by IL-10, such as *Leishmania donovani* (Chandra and Naik, 2008). When macrophages are inactivated by IL-10, fewer pro-inflammatory cytokines and reactive oxygen species that might otherwise cause cell damage are produced (Kessler et al., 2017). Therefore, the current study aimed to evaluate the effect of sodium butyrate on enhancing hepatotoxicity by PPAR signaling in rats.

MATERIALS AND METHODS

Ethical approval

All experiences were approved by the College of Veterinary Medicine Ethical Committee (COVM-6341).

Study design

The investigated samples in the current study were derived from 40 mature Wister Albino female rats aged 8 weeks with a mean weight of 190-200g. The rats were acclimatized in the animal home of the University of Baghdad, College of Veterinary Medicine, Baghdad, Iraq. The period of treatment was 35 days. During the trial, they were kept in well-ventilated rooms within plastic cages, fed a regular pellet diet, and given free access to water for one week. The indoor temperature was 20-25°C and 5% humidity. The rats were exposed to 12-hour alternating light/dark periods throughout the experiment. The bed was changed twice every week. The rats were randomly divided into four equal groups. The first group was considered a control (C), the rats in the second group were orally given sodium butyrate (SB) at a dose of 200 mg/kg daily (Alrafas et al., 2020), and those in the third group were orally subjected to lead acetate (LA) at a dose of 50 mg/kg daily (Sudjarwo et al., 2017). The rats in the fourth group were orally given SB+LA daily**.**

Blood collection and chemical analysis

Blood was collected from each rat using the eye technique (4 ml) because it is an easy technique that does not need any special instruction (van Herck 1998) and is one of the recommended methods of blood collection in rats. The rats in this method were anesthetized by intramuscular injection of Ketamine 60 mg/kg and Xylazine 12 mg/kg. The blood samples were centrifuged (GMBH, Germany) for 15 minutes at 3000 rpm to separate the serum, and the tubes were frozen at -20°C for subsequent analysis. Malondialdehyde (MDA) concentration (µmol/l) was determined by a modified procedure as described by Guidet and Shah, (1989), and the total antioxidant capacity were measured using the commercially available. Malondialdehyde concentration (µmol/l) was determined by a modified procedure as described by Guidet and Shah, (1989), and the total antioxidant capacity were measured using the commercially available ELISA kit (Biosource, USA) utilized according to the manufacturer's instructions. Alanine aminotransferase activity (ALT), alkaline phosphatase (ALP) activity, and aspartate aminotransferase activities (AST) concentrations are determined by a special kit (Spectrum AST, Egypt) using the device spectrophotometer (Sesil, England).

Dosage preparation

Sodium butyrate supplement capsules were purchased from Body Bio (USA). The SB administered dose to rats was 200 mg/kg (Alrafas et al., 2020), while LA obtained from the college laboratory was given at a dose of 50 mg/kg (Sudjarwo et al., 2017).

Quantitative Real-Time PCR

The performed Q-PCR to determine the expression of PPAR-g and IL-10) in the spleen (Table 1) was according to Mohammed et al. (2020). To this end, cDNAs were generated using total RNAs isolated from rats in control, SB, LA, and SB+LA groups using the Real MODTM Green W2 2x qPCR mix. Table 1 indicates the primers used for PPAR-g and IL10 (Lira et al., 2009).

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Table 1. Primer sequences of peroxisome proliferator-activated receptor gamma and interleukin -10

Primers	Reverse	Forward
PPAR-g	5′- GGTCCACAGAGCTGATTCCG -3	5′- GACTGAGTGTGACGACAAGATT -3
IL-10	5′- AGGCTTGGCAACCCAAGTAA -3′	5′- TCCGGGGTGACAATAACTGC -3′
References	5′- GCAGCGATATCGTCATCCAT -3′	5′- CCGCGAGTACAACCTTCTTG -3′,

PPAR-g: Peroxisome proliferator-activated receptor-gamma; IL-10: Interleukin -10

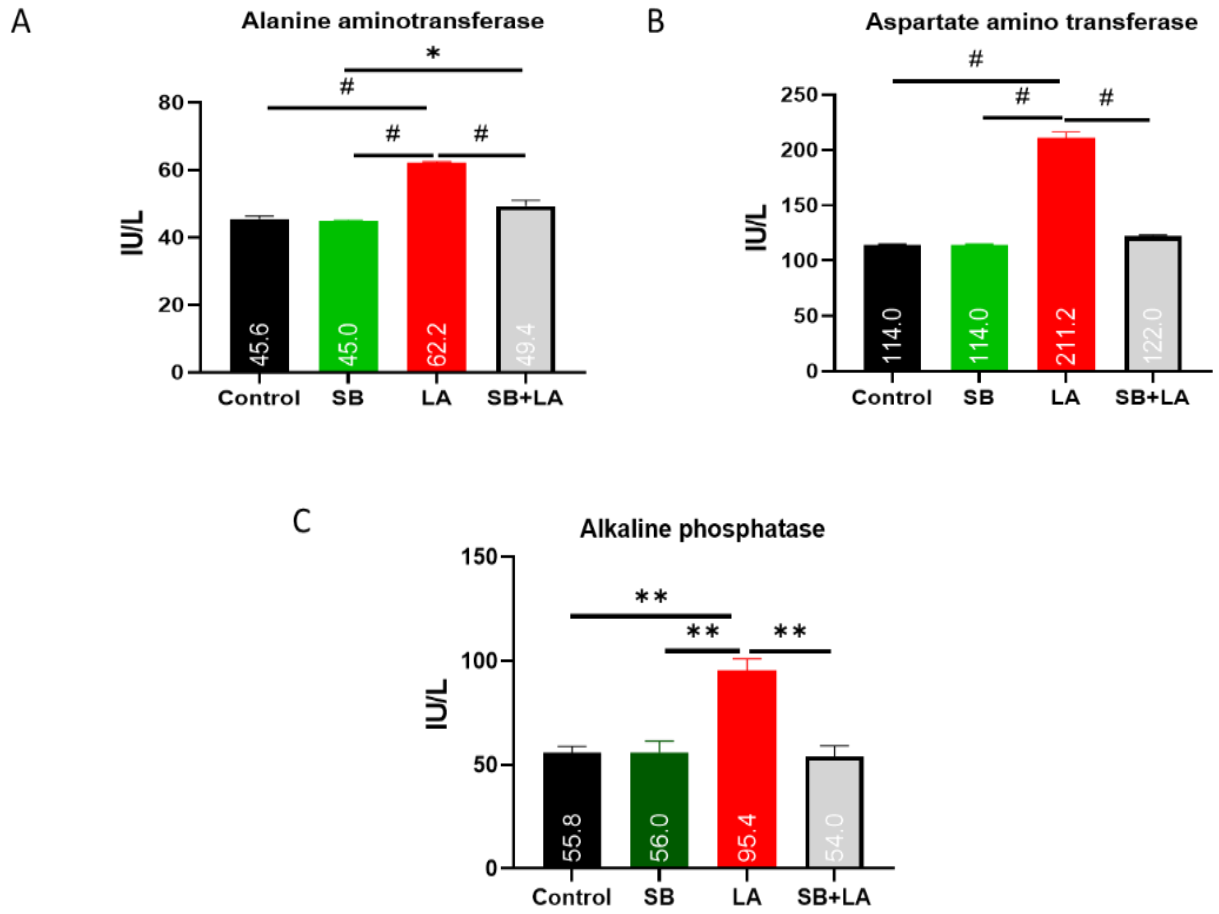
Statistical analysis

The collected data were analyzed in SPSS (Version 22) by using One-Way Analysis of Variance (ANOVA), LSD test was selected to find the significant level between the different data at the level of $p < 0.05$ (Snedecor and Cochran 1980).

RESULTS AND DISCUSSION

Sodium butyrate alleviates hepatotoxicity

As can be seen in Graph 1A, the serum ALT values in rats treated with LA significantly increased ALT activity, compared to the control, SB, and SB+LA groups ($p < 0.05$). In addition, ALT activity significantly decreased in the SB group compared with the LA group and SB+LA after 35 days ($p < 0.05$). Graph 1B shows the mean AST activity of the control and treated groups during the experiment. After 35 days of oral exposure to LA, a significant increase in AST activity was detected, the control, SB, and SB+LA groups ($p < 0.05$). In contrast, three groups of control, SB, and SB+LA indicated non-significant changes in terms of AST ($p > 0.05$). According to Graph 1C, ALP activity is significantly higher in LA group when compared to the control, SB, and SB+LA groups. The results also revealed that there were non-significant differences between the SB therapy and control groups at the end of the experiment ($p > 0.05$).



Graph 1. The effect of sodium butyrate, lead acetate, and their combination on liver function in adult female rats. * and **: Statistical significance between the groups at $p < 0.05$, $p < 0.01$, respectively. **A**: Serum alanine aminotransferase activity (IU/L). **B**: Serum aspartate aminotransferase activity (IU/L). **C**: Serum alkaline phosphatase activity (IU/L). Control: rats received only drinking water, SB: Rats orally received SB 200 mg/kg, LA: Rats orally received lead acetate 50 mg/kg, SB+LA: Rats orally received both sodium butyrate 200 mg\kg orally and LA 50 mg/kg.

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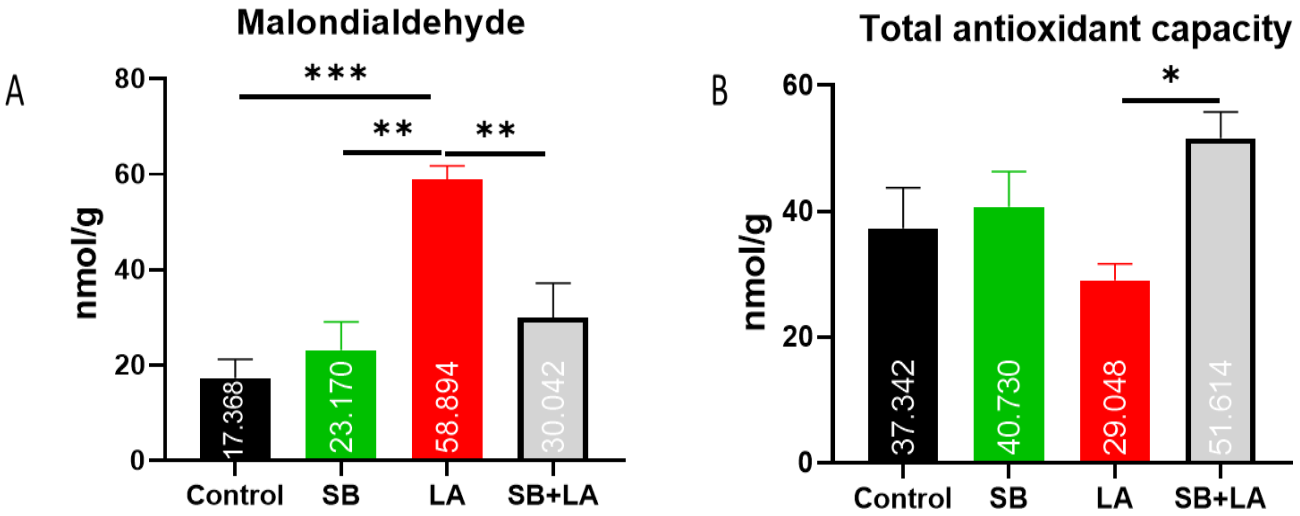
Sodium butyrate effects on the redux status

Graph 2A showed the mean MDA in adult rats' liver tissues after 35 days of treatment in the control and treated groups. Compared to the other experimental groups, there was a significant increase in MDA concentration in the liver of the LA group. Compared to the control group and group treated with only SB ($p < 0.05$).

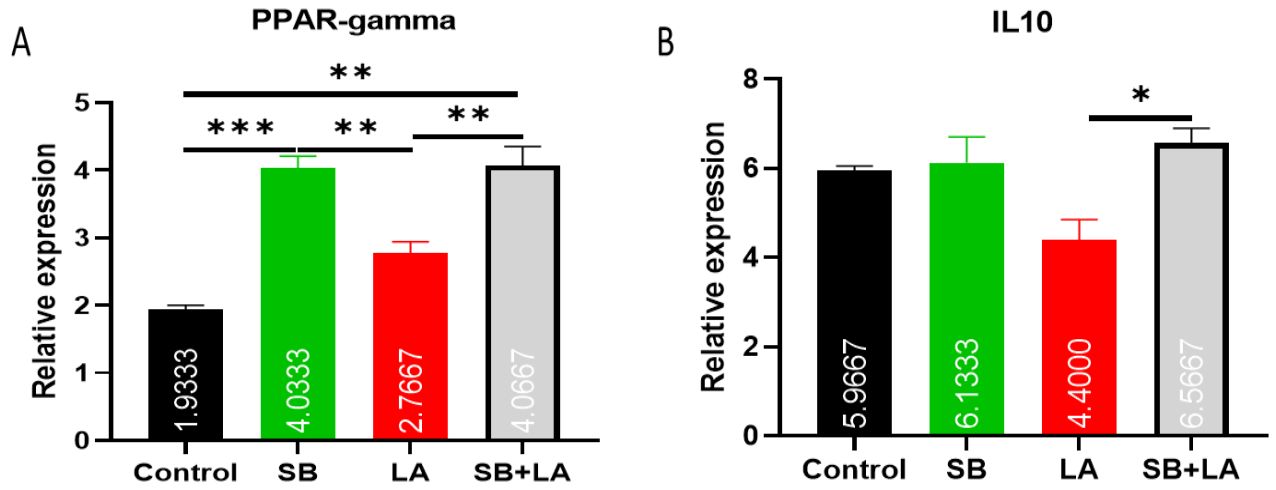
The values of serum total antioxidant capacity in rats exposed to LA and SB orally or SB+LA along the experimental period is clarified in Graph 2B. At 35 days, there were significant differences in the values of serum total antioxidant capacity in all experimental groups as compared to each other ($p < 0.05$). Treatment of rats with LA or SB+LA caused a significant increase in total antioxidant activity after 35 days of the experiment, compared to that of the control and SB groups ($p < 0.05$).



Graph 2. The effect of sodium butyrate, lead acetate, and their combination on redux status in adult female rats. *, **, and ***: Statistical significance between the groups at $p < 0.05$, $p < 0.01$, $p < 0.001$, respectively. **A**: Malondialdehyde concentration in serum (nmol/g). **B**: Total antioxidant capacity concentration in serum(nmol). Control: Rats received only drinking water, SB: Rats orally received sodium butyrate 200mg/kg, LA: Rats orally received lead acetate 50 mg/kg, SB+LA: Rats orally received both sodium butyrate200 mg\kg and lead acetate 50mg/kg.

Validation of PPAR-gamma and IL-10 Genes in the spleen

The sodium butyrate group in Graph 3A showed a significant increase in PPAR-g, compared with a control group and group of rats gavaged with LA only ($p < 0.05$). PPAR-g expression was significantly decreased in the LA group compared with the SB+LAgroup ($p < 0.05$). Moreover, the (SB+LA) group was elevated significantly compared to the control group ($p < 0.05$). Graph 3B showed high elevation in the SB+LA group compared with the LA group ($p < 0.05$). Data showed a significant increase in PPAR-g and IL-10 after SB treatment ($p < 0.05$).



Graph 3. The effect of sodium butyrate, lead acetate, and their combination on PPAR-g and IL-10 in adult female rats. *, **, and ***: Statistical significance between the groups at $p < 0.05$, $p < 0.01$, $p < 0.001$, respectively. **A:** An expression of PPAR- gamma gene. **B:** Expression of IL-10 gene. Control: Rats received only drinking water, SB: Rats orally received sodium butyrate 200mg/kg, LA: Rats orally received lead acetate 50 mg/kg, SB+LA: Rats orally received both sodium butyrate200mg\kg and Lead acetate 50mg\kg.

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Lead acetate exposure considerably enhances AST and ALT in the body (Mohammed, 2010), which can be attributed to an increase in oxidative stress caused by this exposure. The AST-ALT enzymes are special enzymes that can be used to identify liver disease. Those enzymes, commonly found in the cytoplasm of liver cells, leak into the extracellular fluid when membrane permeability is disrupted. However, in case of tissue damage, the cells will rupture, and the enzymes will break down from hepatocytes into the circulatory system, causing their levels in the blood to rise compared to the normal state (Chang et al., 2013). According to previous research, lead exposure is linked to liver damage and increased transaminases and ALP (Shirazinia et al., 2021). In a mouse model of non-alcoholic steatohepatitis (NASH), researchers found that 6 weeks of SB supplementation (0.6 g/kg body weight per day in a liquid diet) prevented the development of NASH, as evidenced by fewer fat-laden hepatocytes, lower expression of pro-inflammatory genes in the liver, and improved insulin signaling compared to untreated control mice (Jin et al., 2016).

Under the effect of lead, oxidative stress manifests itself in two ways of the production of reactive oxygen species (ROS) and the depletion of antioxidant reserves (Flora et al., 2012). Oxidative stress occurs when the body's antioxidant enzymes are depleted and the formation of free radicals. As polyunsaturated fatty acids (PUFA) undergo an increased process of lipid peroxidation, ROS attack all cellular structures, resulting in the loss of cellular and mitochondrial membrane integrity (Jackie et al., 2011). Malondialdehyde is a byproduct of PUFA peroxidation that causes cell membrane damage (Yuniarti et al., 2021). It is also one of the indicators utilized in clinical settings to measure oxidative stress levels. Increased MDA levels in the liver indicate increased lipid peroxidation, which results in tissue damage and the failure of antioxidant mechanisms to prevent the generation of excessive free radicals (Koerniasari et al., 2015).

Furthermore, the current study revealed that pretreatment with SB (200 mg/kg) reduces MDA while increasing superoxide dismutase levels (a key antioxidant enzyme). Furthermore, it was shown that antioxidants reduce HMGB1 expression and prevent pancreatic injury in rats, demonstrating that the release of HMGB1 from cultured hepatocytes is a dynamic process regulated by reactive oxygen species (Zhang et al., 2010). Overproduction of oxygen ROS during oxidative stress can result in lipid peroxidation, protein degradation, and DNA damage (Carocho and Ferreira, 2013). Since mitochondria is the primary source of ROS, it can be targeted by sodium butyrate's antioxidant activity (Zhang et al., 2020). Therefore, under oxidative stress conditions, mitochondria serve as both a substantial generator of ROS and a significant target for oxidative damage (Cao et al., 2020). Impaired mitochondria caused by oxidative stress can release 10 times the amount of ROS as normal mitochondria. The body will use lysosome breakdown to selectively remove damaged mitochondria, a process known as mitophagy (Wang and Klionsky, 2011).

Hepatic cell cancer cell proliferation can be effectively inhibited by SB (Seong and Lee, 2012). The cell cycle's arrest probably explains this effect in the G1 phase, and the decrease in the number of S-phase cells (Xu et al., 2020). The cyclin-dependent kinase inhibitors Cyclin-dependent kinase inhibitors p21 and p27 are crucial for stopping the cell cycle in the G1 phase (Izutani et al., 2012).

In the current report, SB treatment gene expression data seemed to indicate that high expression of anti-inflammatory T-cell factors PPAR-g and IL-10 improved patient inflammation. Increasing PPAR-γ expression and nuclear factor-κB downregulation results suggested that oral supplementation of butyrate could be beneficial as an adjuvant in treating obesity, metabolic syndrome, and insulin resistance (Wen et al., 2021). The production of pro-inflammatory cytokines like TNF-, IL-1, and IL-6 is dose-dependently inhibited by PPAR-agonists (Jiang et al., 1998).

It was indicated that the expression of PPAR-g was closely correlated with the transcriptional activity of IL-10 (Yang et al., 2010). The PPAR-g activation results in Granulocyte colony-stimulating factor production and subsequently Myeloid-derived suppressor cell mobilization (Hegde et al., 2015). There is evidence that PPAR-g plays a key role in regulating Treg cell accumulation and function (Cipolletta et al., 2015). Sodium butyrate treatment can activate PPAR-g signaling, and consequently inducing the Treg cells and MDSCs, which are anti-inflammatory cells and regulate the immune response to decrease lead acetate poising.

CONCLUSION

Sodium butyrate may be considered an antioxidant and has positive effects on liver function. It is therefore suggested to consider the analysis of different doses of sodium butyrate supplements on brain or other soft tissues.

DECLARATIONS

Acknowledgments

This study was funded by a physiology laboratory, and the animals were acclimatized in the animal home of the University of Baghdad's College of Veterinary Medicine, Baghdad, Iraq.

Authors' contribution

Amira Kamil Mohammed, designed all the experiments and Rusul Mowaffaq Ahmed performed all experiments under the supervision of Amira Kamil Mohammed. Rusul Mowaffaq Ahmed collected the data and wrote the draft of the manuscript. Amira Kamil Mohammed contributed to analyzing the data. Amira Kamil Mohammed supervised the work

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from designing to finalizing the manuscript for journal submission. All authors checked and approved the final version of the manuscript for publishing in the present journal

Competing interests

There is no conflict of interest.

Ethical consideration

All of the authors have reviewed the manuscripts for ethical concerns, such as plagiarism, consent to publish, misconduct, data fabrication and/or falsification, duplication of publication and/or submission, and redundancy.

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To cite this paper: Ahmed RM and Mohammed AK (2022). Amelioration of Hepatotoxicity by Sodium Butyrate Administration in Rats. *World Vet. J.*, 12 (3): 323-329. DOI: https://dx.doi.org/10.54203/scil.2022.wvj41