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Original Article

Some histone deacetylase inhibitors protect against dextran sulphate sodium-induced hepatotoxicity in mice

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ABSTRACT

Background and Aims: Ulcerative colitis is an inflammatory bowel disease that affects many people worldwide and has extraintestinal effects. Dextran sulphate sodium (DSS) is a synthetic polysaccharide widely used to model ulcerative colitis in experimental animals. Histone deacetylase (HDAC) inhibitors are molecules that cause changes in gene expression and play a role in many biological events such as inflammatory response formation, cell growth, and differentiation. The aim of this study was to reveal the effects of HDAC inhibitors such as sodium phenylbutyrate (PBA) and suramin on liver morphology, inflammatory mediators, oxidative stress, and antioxidant system in DSS-induced liver injury.

Methods: In this study, 48 male C57BL/6 mice were divided into six groups: control mice; mice administered PBA (150 mg/kg/d, intraperitoneally) or suramin (25 mg/kg/d, intraperitoneally) for 7 days; mice administered 3% DSS orally for 5 days; animals treated with PBA and DSS; and mice treated with suramin and DSS. The effects of PBA and suramin on liver histology were examined microscopically; their impacts on antioxidant parameters and oxidative stress were assessed spectrophotometrically; and their influence on COX-2 and TNF-α expressions was analysed by Western blotting in liver tissues of mice administered DSS.

Results: DSS application resulted in extensive necrosis, increased lipid peroxidation levels, and myeloperoxidase activity, as well as decreased GSH levels and SOD activities in liver tissues. It also increased COX-2 and TNF-α expressions in DSS-induced liver toxicity. PBA or suramin treatment prevented liver injury by mitigating the effects of DSS.

Conclusion: This study showed that PBA and suramin have cytoprotective, anti-inflammatory, and antioxidant effects on DSS-induced hepatotoxicity. Consequently, HDAC inhibitors such as PBA and suramin may be considered effective prophylactic and therapeutic agents against DSS-induced liver injury.

Keywords: Histone Deacetylase Inhibitors, Sodium Phenylbutyrate, Suramin, Dextran Sulphate Sodium, Liver, Mice

INTRODUCTION

Ulcerative colitis is an inflammatory bowel disease (IBD) that begins in the rectum and may spread to the entire colon. It affects not only the gastrointestinal tract but also has extraintestinal effects. Extraintestinal effects commonly seen in IBDs include liver diseases such as nonalcoholic fatty liver disease (NAFLD), primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH) (Klein et al., 2020; Larsen, Bendtzen & Nielsen, 2010). In addition, drugs used for the treatment of IBD cause liver injury as well as side effects such as abdominal pain, sickness, and pancreatitis (Rogler, 2010). Therefore, new and alternative treatment methods are sought to prevent the disease and increase the quality of life of patients. To elucidate the pathogenesis of colitis and develop effective treatment methods, the dextran sulphate sodium (DSS) induced colitis model is widely preferred (Jurjus, Khoury & Reimund, 2004). DSS, a synthetic polysaccharide, is a polyanionic derivative of dextran produced by esterification with chlorosulfonic acid. Because of its large molecular weight, DSS cannot cross cellular membranes and is poorly absorbed. DSS causes inflammation by disrupting the epithelial cell barrier in the colon (Hu et al., 2017).

Chemical compounds that inhibit histone deacetylase enzymes are known as histone deacetylase inhibitors (HDACi). The mechanism of action of HDAC inhibitors involves the inhibition of histone deacetylation. Because of hyperacetylation, the chromatin structure is loosened, which may enable the initiation of gene transcription. Apart from histone proteins, HDACi also affect pathways related to apoptosis, DNA

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repair, mitotic division, redox pathways, cell cycle progression, and angiogenesis. Therefore, HDACi have important effects on physiological and pathological processes, immune response, apoptosis-autophagy control, and inflammation and are considered therapeutic targets for many diseases, including cancer and inflammatory diseases (Tang, Yan & Zhuang 2013). Histone modifications are believed to contribute to the pathogenesis and progression of various liver diseases, including alcoholic liver disease (ALD), metabolic-associated fatty liver disease (MAFLD), viral hepatitis, autoimmune liver disease, and liver fibrosis or cirrhosis (Cai, Gan, Tang, Wu & Gao, 2021). Due to their roles, reversible histone modifications like acetylation and methylation may represent promising therapeutic targets in these diseases (Arechederra et al., 2021; Claveria-Cabello et al., 2020; Liu et al., 2021). Givinostat, an HDACi, potently alleviated diet-induced hepatic steatosis, inflammation, liver injury, and fibrosis (Huang et al., 2022). Administration of the HDAC inhibitor butyrate in mice with alcoholic liver disease (ALD) alleviates pathological damage and inflammation by suppressing lipopolysaccharide (LPS), tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) levels (Zhang et al., 2024).

Sodium phenylbutyrate (PBA) is an aromatic fatty acid salt consisting of an aromatic ring and butyric acid. PBA inhibits HDAC I and IIA classes, which have various physiological functions such as cell proliferation, cell survival, insulin resistance, and gluconeogenesis (Carducci et al., 2001). PBA is known to have immunomodulatory and anti-inflammatory effects (Park, Lee, Lee, Kim & Kim, 2007; Roy et al., 2012). PBA exhibits antioxidant and hepatoprotective effects in CCl4-induced liver injury, reduces liver enzyme levels in the ischaemia/reperfusion mouse model, and demonstrates antiapoptotic and protective effects on the liver (Lee, Marahatta, Bhandary, Kim & Chae, 2016; Vilatoba et al., 2005).

Suramin is an HDAC inhibitor that can suppress the deacetylase activities of sirtuins (SIRTs) (Li & Alam, 2011). Because of its large molecular structure and charge, it cannot pass through the blood-brain barrier, and its half-life is quite long because of its high binding affinity for serum proteins (Bacchi, 2009; Sahu, Sharma, Singla & Panda, 2017). It is thought that the six sulphonate groups in the structure of suramin are responsible for its superoxide and hydroxyl radical scavenging effects (Sahu et al., 2017). Studies in macrophage-like cell lines and collagen-induced arthritis (CIA) model rats have reported that suramin has anti-inflammatory and antioxidant effects (Firsching, Nickel, Mora & Allolio, 1995; Han et al., 2012). In a liver failure model, it was determined that suramin treatment decreased the mortality rate in mice and suppressed the production of TNF- and IL-6 (Goto et al., 2006). Suramin has been reported to exhibit antioxidant effects on the liver in a collagen-induced arthritis model and to possess hepatoprotective and anti-inflammatory properties in ethanol-induced liver damage (He et al., 2013; Sahu et al., 2017).

The literature review revealed no studies demonstrating the effects of PBA and suramin on liver injury caused by DSS. The aim of this study was to reveal the potential effects of PBA and suramin on liver morphology, oxidative stress, antioxidant system, and inflammatory mediators on DSS-induced hepatotoxicity in mice. In order to better analyse the mechanisms of action of PBA and suramin on liver toxicity, we examined the effects of both histone deacetylase inhibitors comparatively.

MATERIALS AND METHODS

Istanbul University Aziz Sancar Experimental Medicine Research Institute Animal Experiments Local Ethics Committee approved this study with decision letter 07 dated 25.02.2016. In this study, 48 C57BL/6 male mice, 8-10 weeks old, were used. Mice were randomly selected and divided into six groups. Group I, control animals were injected with phosphate-buffered saline (PBS, pH 7.4) as the vehicle. Group II mice were injected with 150 mg/kg PBA intraperitoneally (i.p) once a day for 7 consecutive days. Group III, animals were injected with 25 mg/kg suramin (i.p) once a day for 7 sequential days. Group IV consists of mice administered 3% DSS orally for 5 days. Clinical evaluation of colitis was conducted by determining the Disease Activity Index (DAI) in mice (Cooper, Murthy, Shah & Sedergran, 1993). Mice with a DAI score of ≥3 at the end of the experiment in the DSS-given experimental groups were considered to have ulcerative colitis (Ozal-Coskun, 2018). Group V, animals given both PBA and DSS (in the same dose and time). Group VI, animals that were both injected with suramin and given DSS (in the same dose and time). All injections into mice were performed intraperitoneally at the same time every day at 0.1 mL/day. PBA (Sigma SML0309), suramin (Sigma S2671), and PBS i.p. injections were administered for 7 consecutive days. DSS (MP Biomedicals, MW: 36.000-50,000) application was started on the 3rd day, and DSS was applied for 5 days. On the 8th day of the experiment, all animals were sacrificed under anaesthesia. A schematic of the experimental design is shown in Figure 1.

Histopathological assessment

Samples from liver tissue were fixed in Bouin's fixative and embedded in paraffin. Sections of 5 μm thickness taken from paraffin-embedded tissues were stained with Masson's trichrome and Hematoxylin&Eosin dye and examined with an Olympus BX53F light microscope and photographed with an Olympus DP27-CU camera. In the sections, histopathological criteria such as hypertrophy, vacuolisation, pyknotic nucleus, mononuclear cell infiltration, hyperaemia and necrosis were examined. Each criterion was scored between undamaged (0) and severely damaged (3).

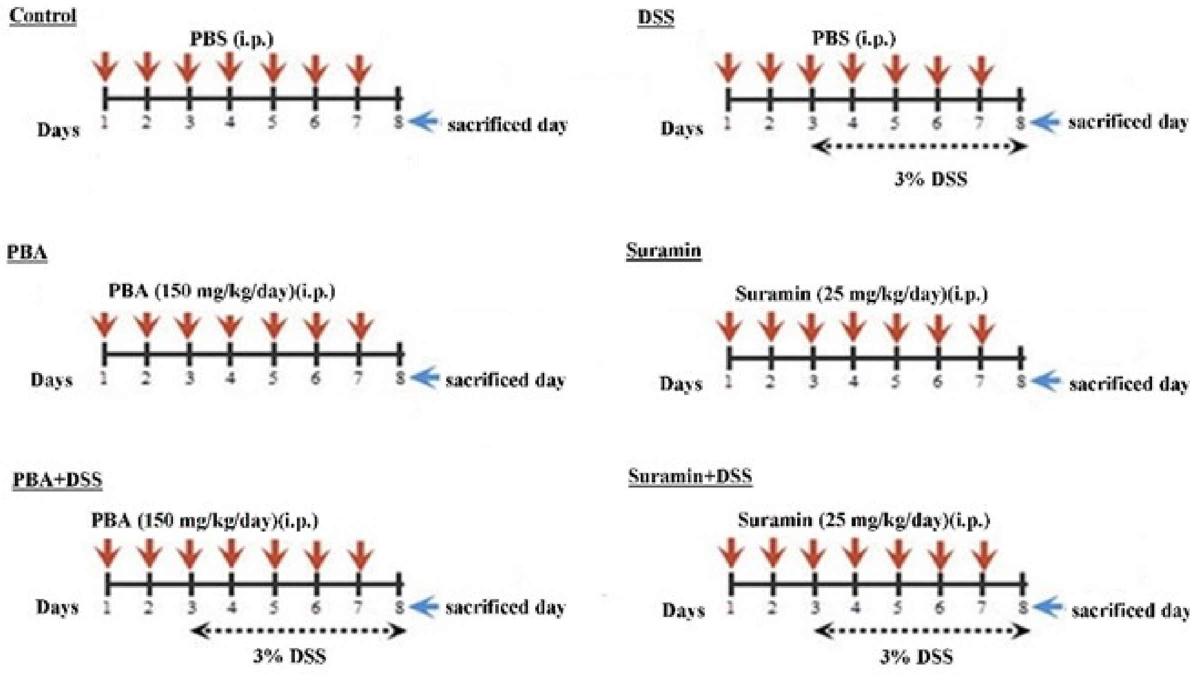

Figure 1. Schematic of the designated experimental groups.

Biochemical analyses

Liver tissue samples were homogenised with 10 mL of 0.9% sodium chloride solution per 1 g of tissue for spectrophotometric analysis. Homogenates were centrifuged at 10.000 g for 15 min (+4°C) and supernatants were used for analysis.

The formation of lipid peroxidation products was assayed by measuring TBARS (thiobarbituric acid reactive substances) levels, which are based on the reaction of malondialdehyde (MDA) with thiobarbituric acid at 532 nm, according to Buege & Aust (1978). The absorbance of the sample was read at 532 nm. The values of TBARS were calculated using an extinction coefficient of 1.56 x 10^5 M^{-1} cm^{-1} and expressed as nmol/mg protein.

SOD activity was assayed using a standard colorimetric assay in which xanthine oxidase serves as a free radical generator and causes the reduction of nitro blue tetrazolium (NBT). SOD inhibits the reduction of NBT by scavenging the free radicals generated by xanthine oxidase (Aruoma, Halliwell, Hoey & Butler 1989). The reaction was measured spectrophotometrically at OD_{560} nm for 10 min at 25°C. Results were expressed as U/mg protein.

Catalase activity was measured using the method of Aebi (1974). Homogenate was added to the cuvette, and the reaction was started by the addition of freshly prepared H_2O_2. The rate of decomposition of H_2O_2 was measured spectrophotometrically from the change in absorbance at 240 nm. The activity of catalase was expressed as U/mg protein.

Tissue MPO activity was measured using a modification of the method described by Hillegass et al (Hillegass, Griswold, Brickson & Albrightson-Winslow, 1990). Briefly, tissue samples were homogenised in ice-cold PBS and centrifuged at 13.000 g for 10 min at 4°C. The supernatants were discarded, and the insoluble pellets were rehomogenized in PBS containing 0.5% hexadecyltrimethylammonium bromide (HTAB). After final centrifugation, the supernatants were used to measure MPO. The changes in absorbance at 460 nm were recorded over 5 min. Results were expressed as units of MPO per g of wet tissue.

The level of reduced glutathione (GSH) was measured in liver tissues by the enzymic recycling procedure using 5,5´-dithiobis-(2-nitrobenzoic acid) (DTNB) and glutathione reductase (DTNB-GSSG reductase recycling assay) as described by Tietze and modified by Anderson (Anderson, 1985). DTNB, distilled water, sample, and stock buffer containing NADPH were mixed in a cuvette and equilibrated to 30°C. To the warmed solution, glutathione reductase was added, and 5-thio-2-nitrobenzoic acid formation was monitored continuously at 412 nm. The GSH content of the aliquot assayed was determined by comparing the rate observed with a standard curve generated using GSH. The results were expressed as nmol of GSH/mg protein.

The protein concentration in the samples was determined using the bicinchoninic acid (BCA) protein assay. The BCA method was performed by optimising the protocol recommended by the manufacturer.

Western blotting

Liver tissue taken for western blot analysis were immediately transferred to liquid nitrogen and stored in a -86°C freezer until the day of analysis. Homogenisation of liver tissue was performed using RIPA buffer containing EDTA and a protease inhibitor. Homogenates were centrifuged at 10.000 g to obtain their supernatants. The amount of protein in the supernatants was determined using the Bradford method (Bradford, 1976). Proteins were separated electrophoretically on a 4-12% Bis-Tris gel (Thermo Fisher Scientific) in MES buffer. Gels were transferred to the nitrocellulose membrane using an iBlot transfer system (Invitrogen, USA). Membranes were blocked with 5% BSA in tris-buffered saline (TBST) for 1 h at room temperature. Primary antibodies were applied to the membranes at +4°C overnight and secondary antibodies for 1 h at room temperature. All antibodies were diluted with 1% BSA (in TBST). The dilution ratio was determined to be 1:2000 for the cyclooxygenase-2 (COX-2) antibody (Novus NB100-689) and 1:1000 for the TNF-α (Abcam ab9739) antibody. β-actin bands were used for normalisation of proteins.

Statistical analysis

All data were evaluated using the SPSS 28.0 statistical programme. The normality test and homogeneity test of variances were applied to the data of all parameters. For the data of all parameters, an independent t-test was used between pairs, following the one-way ANOVA test. The results were given as "mean ± standard error". $p<0.05$ was considered statistically significant.

RESULTS

Histopathological findings

Images of liver sections stained with Masson's trichrome dye and findings regarding liver damage scoring are shown in Figure 2.

Normal histological appearance predominates in the liver sections of the control, PBA, and suramin group mice. Findings such as necrosis, mononuclear cell infiltration, and hyperaemia were not observed in the liver tissue sections of these mice. The finding of widespread severe necrosis in the liver tissue of DSS group mice. In addition, it has been determined that DSS application causes mononuclear cell infiltration in the liver, hyperaemia in blood vessels, and moderate vacuolisation and pyknotic nucleation formation in hepatocytes. When the liver tissue of the DSS+PBA and DSS+suramin group mice are examined, the liver injury caused by DSS is significantly reduced. While necrosis, mononuclear cell infiltration and hyperaemia findings are almost never observed in the liver sections of these two groups, slight vacuolisation was occasionally observed in hepatocytes.

Considering all these parameters, it was determined that the liver damage score in the DSS group increased significantly compared with that in the control group ($p<0.001$). It appears that treatment with PBA or suramin significantly reduces the damage caused by DSS in the liver ($p<0.001$).

Findings of the biochemical analysis

The findings of the biochemistry analysis of all groups are shown in Figure 3.

GSH levels in liver tissue were significantly decreased in the DSS group mice compared with the control group mice ($p<0.001$). There was a significant decrease in GSH levels in the group to which PBA was applied alone compared with the control group ($p<0.001$). PBA treatment caused an increase in low GSH levels caused by DSS in the liver; however, this increase was not statistically significant. In addition, a significant increase in GSH levels was detected in the Suramin group compared with the control group ($p<0.001$). The highest GSH levels among all groups were measured in mice in this group. Suramin treatment of DSS group mice also caused a statistically significant increase in decreased GSH levels ($p<0.001$). GSH levels decreased due to DSS but approached the control group levels after suramin treatment.

When all groups were examined, it was determined that there were higher MDA levels in the liver tissue of the DSS group. In this group, MDA levels were significantly increased compared with the control group ($p<0.01$). In addition, a significant increase in MDA levels was detected in the PBA group compared with the control group ($p<0.05$). It was observed that the administration of PBA to the DSS group did not decrease the increased MDA levels. There was no significant difference in MDA levels between the suramin group and the control group. In addition, it was determined that suramin treatment of DSS group mice caused a significant decrease MDA level ($p<0.001$).

Among the groups, the highest MPO activity in liver tissue was observed in the DSS group. The MPO activity in the DSS group increased significantly compared with the control group mice ($p<0.001$). MPO activity in the PBA group increased significantly compared with the control group ($p<0.01$), whereas there was no significant difference in the suramin group when compared with the control group. Separately administration of both PBA and suramin to DSS group mice significantly reduced the activity of MPO increased with DSS in the liver ($p<0.001$). There was a significant decrease in SOD activity in the liver tissue of the DSS group compared with the control group ($p<0.05$). No significant changes in SOD activity were detected between the PBA and suramin groups compared with the control group. Treatment of PBA ($p<0.01$) and suramin ($p<0.001$) to the DSS group caused a significant increase in SOD activity in the liver homogenates.

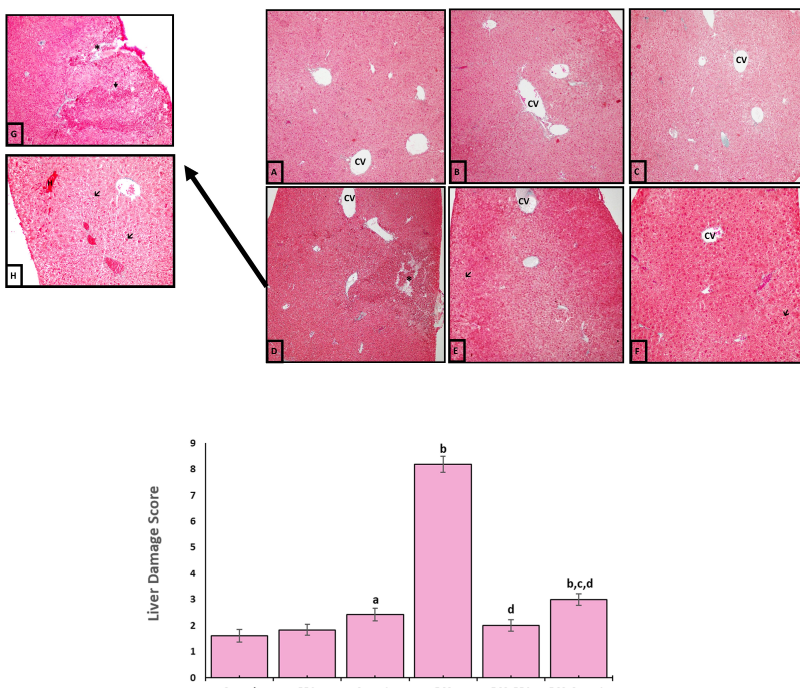

Figure 2. Masson's trichrome staining in the liver of mice in all groups. **A:** Control group, **B:** PBA group, **C:** Suramin group, **D:** DSS group, **E:** DSS + PBA group, **F:** DSS + suramin group. (Original magnification x100). **G:** Widespread necrotic areas on the liver of the DSS-given group, **H:** Severe hyperaemia and vacuolisation observed on the liver section of DSS-given mice. (Original magnification x200). Central vein (CV), Mononuclear cell infiltration (→), necrosis (*), hyperaemia (H), vacuolisation (→). Findings of liver damage score. a: (p<0.05) vs. control group b: (p<0.001) vs. control group c: (p<0.05) vs. PBA group d:(p<0.001) vs. DSS group.

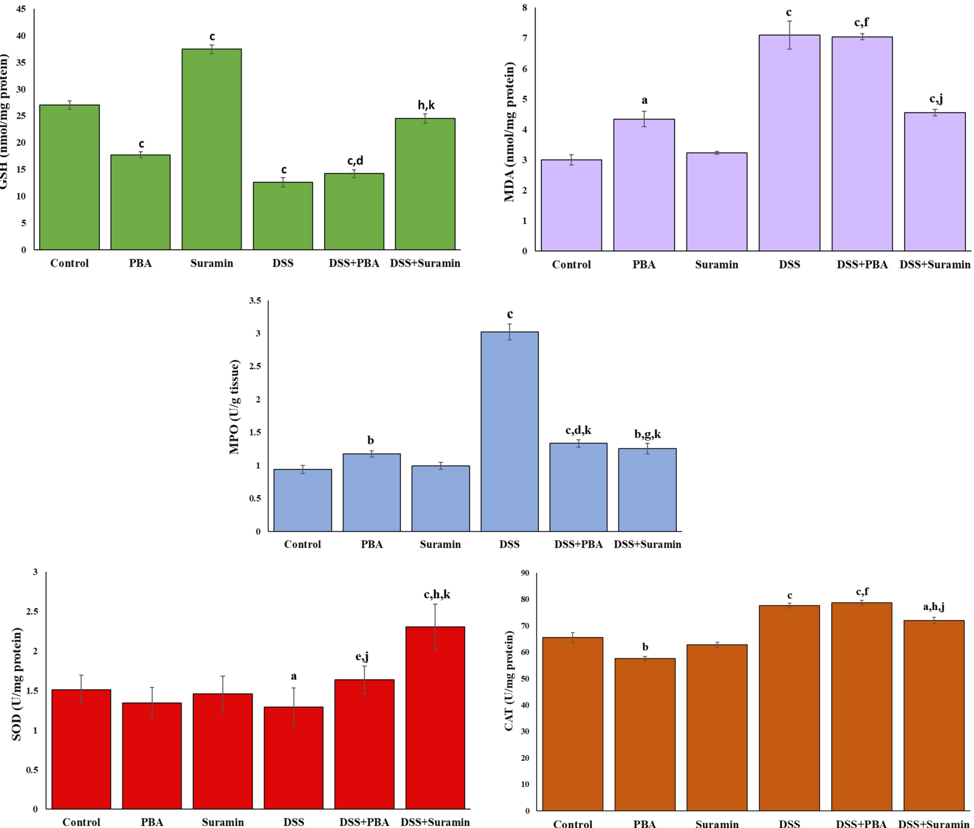

Figure 3. GSH, MDA, and MPO levels and SOD and CAT enzyme activities in liver homogenates according to groups. (Mean ± Standard error). a: (p<0.05) vs. control group; b: (p<0.01) vs. control group; c: (p<0.001) vs. control group; d: (p<0.05) vs. PBA group; e: (p<0.01) vs. PBA group; f: (p<0.001) vs. PBA group; g: (p<0.01) vs. suramin group; h: (p<0.001) vs. Suramin group; i: (p<0.05) vs. DSS group; j: (p<0.01) vs. DSS group; k: (p<0.001) vs. DSS group.

DSS administration did not decrease CAT activity in liver tissue. CAT activity in the PBA group showed a significant decrease compared with that in the control group ($p<0.01$). However, the decrease in the suramin group compared with the control group was not statistically significant. It was determined that PBA treatment of the DSS group caused a non-significant increase in CAT activity compared with the DSS group, but it significantly increased CAT activity compared with the control ($p<0.001$) and PBA ($p<0.001$) groups. Although suramin application to the DSS group caused a significant increase in CAT activity compared with the control ($p<0.05$) and suramin ($p<0.001$) groups, it was determined that there was a decrease in CAT activity in this group compared with the DSS group ($p<0.01$).

Changes in COX-2 and TNF- α protein expression levels

The COX-2, TNF-α and β-actin bands of liver tissue and the COX-2 and TNF-α expression according to the groups are shown in Figure 4.

There was a significant increase in COX-2 and TNF-α expression in the liver tissue of the DSS group compared with the control group ($p<0.001$). It was determined that PBA treatment of the DSS group caused a significant decrease in both COX-2 ($p<0.01$) and TNF-α ($p<0.001$) expression. Suramin treatment also caused a significant decrease in COX-2 ($p<0.001$) and TNF-α ($p<0.001$) expression, which were increased by DSS, similar to PBA.

DISCUSSION

Inflammatory bowel diseases (IBD), such as ulcerative colitis, have extracolonic effects. The most common and serious extracolonic effects of IBD include hepatobiliary abnormalities (Lichtenstein, 2011). It has been found that 5-10% of patients with IBD develop hepatobiliary disorders (Memon, Memon & Memon, 2000). In addition, it has been reported that drugs used for the treatment of IBD can also cause liver damage. (Koller et al., 2017; Mazza et al., 2021). New and effective treatment methods for IBD are sought because of the risk of developing colon cancer, the decreased quality of life in patients, and the serious side effects of the drugs used. Approximately 70% of the liver's blood supply comes from the portal vein, and thus, liver more responsive to the mediators originating from intestine (Adawi, Molin & Jeppsson, 1999).

The pathogenesis of IBD-associated liver injury is typically linked to increased intestinal mucosal permeability. In conditions like ulcerative colitis, the heightened release of inflammatory mediators and toxins in colon tissue triggers inflammation-related signalling pathways upon reaching the liver (Duan et al., 2020). These activated pathways lead to increased production of pro-inflammatory cytokines in the liver, which stimulates hepatocyte damage and inflammation. Primary sclerosing cholangitis (PSC) is typically characterised by fibrosis due to persistent inflammation in the liver, leading to cirrhosis and failure. It is the most common hepatobiliary disease associated with inflammatory bowel diseases (IBDs), with approximately 70-80% of PSC patients also having IBD. (Broomé & Bergquist, 2006). Autoimmune hepatitis (AIH) is characterised by necrosis, severe portal inflammation, and lymphocyte infiltration on liver histology and has been particularly described in patients with ulcerative colitis. (Trivedi & Chapman, 2012).

DSS-induced colitis model is the most widely used animal model to study the pathogenesis and potential therapeutic agents of ulcerative colitis. Various studies have reported histopathological findings such as necrosis, inflammation, and fibrosis in the liver tissues of experimental animals administered DSS to induce colitis (Trivedi & Jena, 2013; Farombi et al., 2016; Li et al., 2021). DSS-induced colitis is characterised by inflammation in the colon and disruption of the mucosal barrier. After 5 days of DSS administration to mice, an increase in the DAI score, inflammation, and oxidative damage in the colon were clearly observed (Ozal-Coskun, 2018). In the current study, DSS-induced hepatotoxicity was examined as an extraintestinal effect of colitis. This study determined that DSS had hepatotoxic effects by causing necrotic damage, which is consistent with findings in the literature. Histone deacetylase inhibitors (HDACi) are known to exhibit anti-inflammatory effects in some inflammatory disease models (Glauben et al., 2006; Sailhamer et al., 2008; Gillespie et al., 2012). PBA is used as a drug in urea metabolism disorders and in the treatment of various diseases. It is an HDACi that has been tested for clinical use (Maestri, Brusilow, Clissold & Bassett, 1996). In our study, it was observed that PBA treatment of mice at a dose of 150 mg/kg for 7 days suppressed the histopathological damage caused by DSS in the liver and showed protective effects. Suramin is an HDACi used for therapeutic purposes against African trypanosoma. In our study, it was determined that suramin, used at a dose of 25 mg/kg for 7 days, reduced the damage to the liver that increased with DSS application, similar to PBA. PBA exhibits anti-inflammatory and anti-apoptotic effects in various liver injury models, protecting the liver against damage and fibrosis. (Wang et al., 2013; Shimizu et al., 2014; Lee, Marahatta, Bhandary, Kim & Chae, 2016). Similarly, studies have shown that suramin has antiapoptotic, anti-inflammatory, antioxidant, and hepatoprotective effects on the liver (Doggrell, 2004; He et al., 2013; Tayel et al., 2014). However, no study has investigated the effects of PBA or suramin on liver injury in DSS-induced ulcerative colitis. In our study, we comparatively examined the antioxidant and anti-inflammatory effects of PBA and suramin on liver injury caused by DSS. Our goal was to understand the protective effects of these agents on liver injury and to explore the potential therapeutic effects of HDAC inhibitors on liver diseases.

MPO is considered an indicator of inflammatory damage and a biomarker of leukocyte infiltration (Zheng, Gao & Wang,

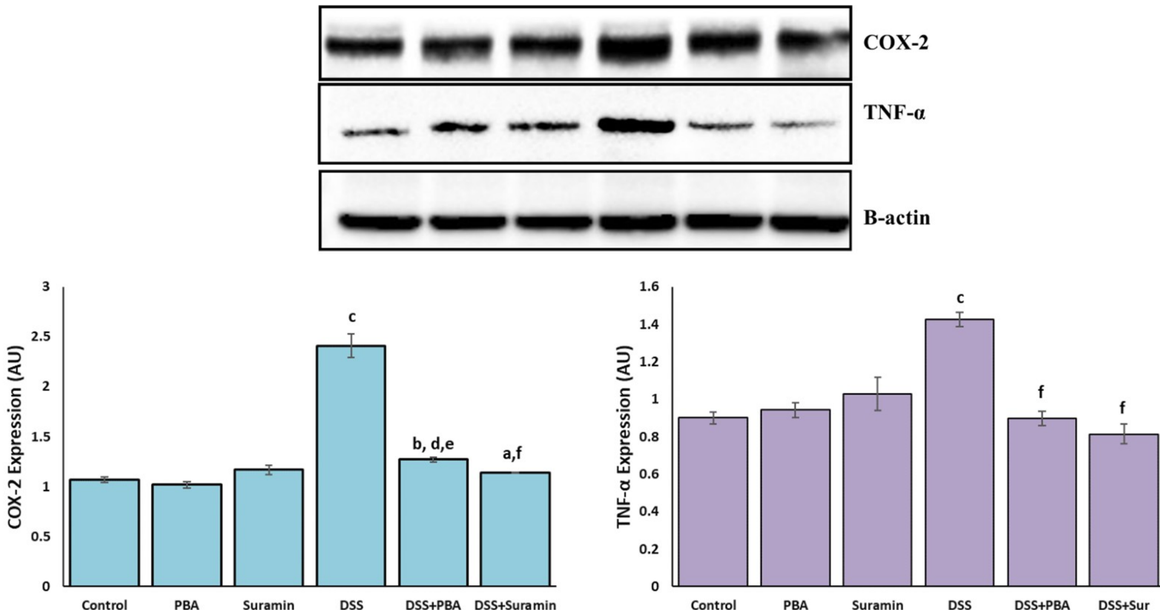

Figure 4. COX-2, TNF-α and β-actin bands of liver tissue and the COX-2 and TNF-α expression level of all groups analysed by western blotting. The data are presented as mean ± standard error (SE). a: ($p<0.05$) vs. control group, b: ($p<0.01$) vs. control group, c: ($p<0.001$) vs. control group, d: ($p<0.001$) vs. PBA group, e: ($p<0.01$) vs. DSS group, f: ($p<0.001$) vs. DSS group.

2000). DSS causes an increase in MPO levels in the colon by stimulating neutrophil infiltration (Sangaraju et al., 2019; Zhao et al., 2022). Oral DSS administration similarly increases MPO levels in the liver tissue. Previous studies have shown that DSS application leads to a decrease in the activities of antioxidant enzymes, including SOD and CAT, in tissues and an increase in the level of MDA, a marker of lipid peroxidation. In the DSS colitis model, it was determined that GSH levels decreased, whereas MPO and MDA activities increased as a result of liver damage. (Trivedi & Jena, 2013). In another study, it was reported that DSS application increased MPO and lipid peroxidation levels and decreased GSH levels and activities of enzymes such as SOD, CAT, and GPx in the liver and colon (Farombi et al., 2016). Several studies have demonstrated that DSS administration leads to a reduction in antioxidant enzyme activities and GSH levels in the liver and an increase in hepatic MPO, LDH, and MDA activities, thereby suppressing the antioxidant system and causing oxidative damage in the liver. (Mouzaoui, Rahim & Djerdjouri, 2012; Rtibi et al., 2016). The increase in MPO levels observed in the liver in our study is an indicator of inflammatory damage caused by leukocyte infiltration in mice treated with DSS. In addition, there was a decrease in SOD levels along with decreased GSH levels and increased MDA levels in the liver tissue in the DSS group compared with the control group. These findings indicate that DSS causes oxidative damage in the liver. PBA has been reported to protect tissue against oxidative damage by reducing the levels of MDA and MPO, which increase as a result of damage in various tissues, and by increasing the levels of antioxidant enzymes (Vilatoba et al., 2005; Daosukho et al., 2007; Jangra, Sriram & Lahkar, 2016). Similarly, suramin has been shown to exhibit antioxidant activity by reducing the levels of MPO and MDA, which increase due to oxidative damage in the liver, and by elevating the levels of SOD (Tayel et al., 2014; Sahu et al., 2017). In our study, it was determined that PBA and suramin application to groups administered DSS decreased MPO levels. Suramin significantly reduced elevated MDA levels in liver tissue, whereas PBA administration did not effectively reduce lipid peroxidation levels. In this study, the fact that PBA and suramin caused a decrease in GSH levels and an increase in SOD enzyme activity with DSS is consistent with the literature. Our study found that DSS application did not decrease CAT levels in the liver tissue. When comparing the effects of the two HDAC inhibitors on the antioxidant system and oxidative stress, suramin was observed to increase GSH levels and SOD enzyme activities in liver tissue more than PBA. In addition, suramin was more effective than PBA in reducing MPO and MDA levels. Considering these findings, we can conclude that HDAC inhibitors such as PBA and suramin protect liver tissue against oxidative damage caused by DSS.

Cytokines are mediators that play a key role in the initiation and development of inflammation and the treatment of inflammatory diseases (Strober & Fuss, 2011). TNF-α is a key pro-inflammatory cytokine in inflammatory bowel diseases, stimulating the release of inflammatory mediators and reactive oxygen species (ROS) (Brown & Mayer, 2007). Mucosal levels of TNF-α are increased in patients with IBD, and anti-TNF-α therapies have been developed with their inhibition and neutralisation (Järnerot, et al., 2005). COX-2 is an enzyme that can stimulate some cytokines, including TNF-α, and is responsible for the formation of prostanoids. It has been reported that

DSS administration increases the levels of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and COX-2 in liver tissue (Trivedi & Jena, 2013; Farombi et al., 2016). In the acute colitis model induced by 2.5% DSS, the relative mRNA expression levels of inflammatory mediators such as TNF-α, IL-1β, and IL-6 increased in liver tissue (Rohwer, et al., 2023). Various studies have determined that PBA and suramin have anti-inflammatory effects (Novales-Li, 1996; Ono et al., 2014). It has been reported that TNF-α and IL-6 levels, which increase as a result of liver tissue damage, decrease as a result of PBA application (Vilatoba et al., 2005; Qiao, Qian, Wang, Ma & Wang, 2014). Suramin has also been observed to reduce increased levels of cytokines such as TNF-α, IL-1β, and IL-6 in both liver tissue and serum in liver injury models (Goto et al., 2006; He et al., 2013). In our study, it was determined that DSS application caused a significant increase in both COX-2 and TNF-α levels in liver tissue compared with the control group. It was observed that PBA or suramin treatment led to a decrease in COX-2 and TNF-α levels, which increased with DSS. Two different HDACi showed similar effects in suppressing increased COX-2 and TNF-α levels in liver tissue with DSS.

CONCLUSION

As a result, HDAC inhibitors such as PBA and suramin prevent hepatotoxicity by exhibiting cytoprotective, antioxidant, and anti-inflammatory effects on liver injury caused by DSS. Considering these properties, PBA and suramin may be considered effective prophylactic and therapeutic agents against colitis-induced liver injury because they do not cause hepatotoxicity and possess cell-protective effects.

Ethics Committee Approval: İstanbul University Aziz Sancar Experimental Medicine Research Institute Animal Experiments Local Ethics Committee approved this study with decision letter 07 dated 25.02.2016.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study: C.O.C., P.A.; Data Acquisition: C.O.C., N.O., A.U.; Data Analysis/Interpretation: P.A., N.O.; Drafting Manuscript: C.O.C.; Critical Revision of Manuscript: C.O.C., P.A.; Final Approval and Accountability: C.O.C., P.A., N.O., A.U.

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