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Original Article

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Impact of sodium metabisulfite on the structural, hematological, and enzyme dynamics in liver and spleen of Wistar rats

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Abstract

***Background & Aims*:** Sodium metabisulfite (SMB) is widely used in the pharmaceutical and food industries for its antioxidant and antimicrobial properties; however, its potential to generate toxic oxidants raises concerns. This study aimed to investigate the structural alterations, blood parameters, and enzyme dynamics associated with SMB exposure in the liver and spleen of Wistar rats.

***Materials & Methods*:** Twenty-four juvenile Wistar rats were randomly divided into four groups consisting of six rats each: Group 1 (control) received 0.5mL normal saline; Group 2 was administered 100 mg/kg SMB; Group 3 received 300 mg/kg SMB; and Group 4 was given 500 mg/kg SMB. The administration was conducted orally over a period of 28 days, after which the rats were euthanized for tissue collection. Blood samples were obtained to analyze red blood cell (RBC) count, hemoglobin (Hb) count, platelets (PLT) count, and white blood cell (WBC) count, while liver and spleen tissue samples were collected for alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransaminase (AST) assays, along with histopathological examination using haematoxylin and eosin staining.

***Results*:** In rats given SMB at 500mg/kg, RBC levels were significantly lower compared to the control and SMB 100 mg/kg groups. PLTs were significantly reduced in the SMB 300 mg/kg and 500mg/kg groups. No significant differences were observed in WBC and Hb levels. ALP, alanine aminotransferase, and aspartate aminotransferase levels were significantly higher in rats given SMB at varying doses, with higher doses causing greater elevation. Liver histology revealed hepatocellular necrosis at 500 mg/kg, while spleen histology showed disrupted architecture at the same dose.

***Conclusion*:** The study highlights significant hematological and hepatic effects of varying doses of SMB in rats, emphasizing potential toxicity and necessitating further safety assessments.

***Keywords*:** Blood, Histopathological analysis, Liver enzymes, Sodium metabisulfite, Spleen, Toxicity

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Introduction

Sodium metabisulfite (SMB) is a versatile compound widely used as an antioxidant and preservative in the pharmaceutical and food industries. In pharmaceuticals, it prevents oxidation in injectable formulations (1), while in food, it acts as an antimicrobial and antioxidant agent, detectable via electrochemical sensors (2). Despite its beneficial applications, SMB exhibits dual behavior, acting as both an antioxidant and a prooxidant under certain conditions (3).

Growing evidence suggests that SMB may pose significant health risks. In humans, it has been linked to oxidative stress, immune dysfunction, and organ damage, manifested through decreased antioxidant enzyme activities, increased lipid peroxidation (4), and alterations in biochemical, hematological, and physiological parameters (5). Additionally, SMB exposure has been associated with allergic dermatitis, respiratory allergies, and potential carcinogenic, developmental, and atherogenic effects (6). High doses exacerbate these effects, inducing apoptosis in gastric tissue (7) and distorting reproductive structures in animals (8).

In animal models, SMB's toxicity is well-documented. It induces genotoxic effects in mouse tissues (9), promotes oxidative stress in rat liver and kidney (10), and disrupts endocrine function by reducing testosterone levels in male mice (11). Notably, subchronic exposure alters immune responses and hematological parameters in Wistar rats (5), while ghrelin has been shown to mitigate SMB-induced liver damage (7). However, some studies report inconsistent effects, such as unchanged malondialdehyde levels despite acetylcholinesterase inhibition (12-15).

The liver and spleen are critical targets for SMB toxicity due to their roles in metabolism, detoxification, and immune regulation. SMB disrupts hepatic enzyme activities (e.g., alkaline phosphatase (ALP) (16) and induces endoplasmic reticulum stress (7), while its impact on splenic function remains underexplored. Given these organs' centrality to homeostasis, understanding SMB's effects on them is essential for risk assessment.

This research aims to provide valuable insights into the structural alterations, blood parameters, and enzyme dynamics associated with SMB exposure in vital organs, particularly the liver and spleen. Given the pivotal roles of the liver and spleen in metabolism, detoxification, and immune responses, any adverse effects on these organs could have significant health consequences. Furthermore, elucidating the mechanisms underlying oxidative stress induction and enzyme dynamics will provide valuable insights into the potential toxicity of SMB and inform regulatory decisions.

Materials & Methods

Animals

A total of 24 juvenile female Wistar rats were obtained from Olaolu Animal Husbandry in Ogbomoso, Nigeria, and housed at the animal facility of Adeleke University in Ede, Nigeria. The animals were kept in standard plastic cages with ventilated metal lids under controlled environmental conditions: temperature at 22 ± 2°C, relative humidity of 50-60%, and a 12-hour light/dark cycle. Following a 7-day acclimatization period to allow adjustment to the new environment, the rats were randomly divided into four experimental groups of six animals each. Throughout both the acclimatization and experimental periods, all animals had ad libitum access to standard rodent pellet diet and fresh water. The study protocol was approved by the Research Ethics Committee of Adeleke University (Approval No. 00690), in accordance with institutional and international guidelines for animal welfare.

Experimental Design

Following the completion of the acclimatization phase, the rats were randomly divided into four groups of six animals each. Oral treatments were administered over 28 consecutive days as follows: Group 1 (control) received 0.5 mL of distilled water daily. Groups 2–4 received SMB at doses of 100, 300, and 500 mg/kg body weight, respectively. The SMB solutions were freshly prepared each day by dissolving pharmaceutical-grade

SMB powder (Sigma-Aldrich, purity ≥ 97%) in distilled water to achieve the required concentrations. Solution stability was maintained by preparing the doses immediately before administration and protecting them from light exposure. The selected dosage regimen was based on previous work by Amedu and Ajayi (8), which demonstrated dose-dependent effects within this range. All treatments were administered by oral gavage between 8:00 and 10:00 AM daily, with the volume adjusted according to individual body weights measured every third day.

Blood Collection and Analysis

After the administration of substances, each rat underwent cervical dislocation and thoracotomy. Blood was collected via cardiac puncture into EDTA test tubes from all animals grouped accordingly. The collected blood samples were promptly stored at −20 °C until hematologic parameters were assessed using an auto hematology analyzer (Seattle, USA). Parameters examined included red blood cell (RBC), hemoglobin (Hb), platelets (PLT), and white blood cell count (WBC) (17).

Biochemical Assay

Liver tissues (each at 10% w/v) not fixed with a fixative underwent PBS washing followed by homogenization using a Teflon Potter–Elvehjem homogenizer on ice to create a homogenate solution. This solution was then centrifuged (at 4,000g for 5 minutes), and the resulting supernatant was utilized to determine the levels of ALP, alanine aminotransferase (ALT), and aspartate aminotransaminase (AST). The assessment of ALP, ALT, and AST levels followed the protocols provided with assay kits obtained from Sigma-Aldrich (St Louis, MO, USA). Results are expressed in IU/L.

Histopathology Test

The rats designated for histopathological assessments were anesthetized via intraperitoneal injection of ketamine at a concentration of 50mg/mL. Subsequently, euthanasia was performed by decapitation, and the liver and spleen of each rat were meticulously extracted and thoroughly rinsed in normal saline. Following this, the collected tissues were fixed in 10% neutral formalin. Tissue processing and staining with haematoxylin and eosin (H & E) followed the procedures outlined in Bancroft and Gamble (18). Stained sections were observed under a light binocular microscope (Olympus, New Jersey, USA) equipped with an Amscope camera (MD500, CA, USA).

Statistical Analyses

Statistical analyses and graph adjustments were conducted using Graph Pad Prism version 7.0 for Windows. Differences in significance were assessed through one-way ANOVA, followed by Tukey's post-hoc test. Results are presented as mean ± standard deviation in both text and figures. Statistical significance was set at $P < 0.05$.

Results

Impact of Sodium Metabisulfite on Blood

The level of RBC was significantly lower ($P < 0.05$) in the group of rats administered SMB at 500 mg/kg compared to the control and SMB 100 mg/kg groups. No significant difference was observed in RBS levels among the control, SMB 100 mg/kg, and SMB 300 mg/kg groups (Table 1). The WBC count in all the SMB-treated groups (100 mg/kg, 300 mg/kg, and 500 mg/kg) showed no significant difference ($P > 0.05$) compared to the control group (Table 1). Furthermore, platelet counts in the groups administered SMB at 300 mg/kg and 500 mg/kg were significantly lower ($P < 0.05$) compared to the control group. Additionally, these groups (SMB 300 mg/kg and 500 mg/kg) had lower PLT ($P < 0.05$) compared to the SMB 100 mg/kg group. However, the platelet level in the SMB 100 mg/kg group was not significantly ($P > 0.05$) different from the control group (Table 1). Finally, the Hb count in all SMB-treated groups (100 mg/kg, 300 mg/kg, and 500 mg/kg) showed no significant difference ($P > 0.05$) compared to the control group (Table 1).

Table 1. Mean values of hematologic parameters in the experiment

Parameters	Control	SMB (100mg/kg)	SMB (300mg/kg)	SMB (500mg/kg)
RBC ($\times 10^6$/µl)	8.5 ± 0.2	8.1 ± 0.07	7.5 ± 0.3	6.4 ± 0.6 [a, b]
WBC ($\times 10^3$/µl)	13.4 ± 1.7	13.4 ± 1.8	13.0 ± 1.3	12.9 ± 1.0
PLT ($\times 10^3$/µl)	586.7 ± 67	530.7 ± 50	512.3 ± 16 [a, b]	502.8 ± 61 [a, b]
Hb (g/dl)	13.8 ± 0.6	13.6 ± 0.2	13.5 ± 0.7	12.8 ± 0.4

Values are the means ± SD; SD = standard deviation; SMB = sodium metabisulfite; RBC: red blood cell; RBC: red blood cell count; Hb: hemoglobin; PLT: Platelets. [a]*P-value* less than 0.05 vs control; [b]*P-value* less than 0.05 vs SMB (100mg/kg). n = 6 rats.

Impact of Sodium Metabisulfite on Biochemical Markers of Hepatocellular and Hepatobiliary Injury

The ALP level (Table 2) was significantly elevated ($P < 0.05$) in the group of rats administered SMB (500 mg/kg, 300 mg/kg, and 100 mg/kg) compared to the control group. Additionally, the SMB 300 mg/kg and 500 mg/kg groups exhibited higher ($P < 0.05$) ALP levels compared to the SMB 100mg/kg group. There was no significant difference ($P > 0.05$) observed when comparing the ALP levels between the SMB 500mg/kg and 300 mg/kg groups (Table 2). Similar trends were observed in the levels of alanine aminotransferase and aspartate aminotransferase (Table 2). Both enzymes were significantly elevated ($P < 0.05$) in the groups of rats administered SMB (500 mg/kg, 300 mg/kg, and 100 mg/kg) compared to the control group. Furthermore, the SMB 300mg/kg and 500mg/kg groups displayed higher ($P < 0.05$) levels of alanine aminotransferase and aspartate aminotransferase compared to the SMB 100 mg/kg group. No significant difference ($P > 0.05$) was observed when comparing the levels of alanine aminotransferase and aspartate aminotransferase between the SMB 500mg/kg and 300mg/kg groups (Table 2).

Table 2. Biochemical markers of hepatocellular and hepatobiliary injury

Enzymes	Control	SMB (100 mg/kg)	SMB (300 mg/kg)	SMB (500 mg/kg)
Alkaline phosphatase (IU/L)	70 ± 11	120 ± 31[a]	260 ± 50 [a, b]	270 ± 30 [a, b]
Alanine aminotransferase (IU/L)	110 ± 17	170 ± 20 [a]	280 ± 40 [a, b]	300 ± 25 [a, b]
Aspartate aminotransferase (IU/L)	90 ± 12	250 ± 30 [a]	310 ± 50 [a, b]	460 ± 50 [a, b]

Values are the means ± SD; SD = standard deviation; SMB = sodium metabisulfite. [a]*P-value* less than 0.05 vs control; [b]*P-value* less than 0.05 vs SMB (100mg/kg). n = 5 rats.

Histopathology Observations

The liver photomicrographs (Figure 1) portray hepatocytes in the control group exhibiting normal sinusoids extending from a central vein toward the portal triad. Neither the SMB 100 mg/kg nor the 300 mg/kg groups showed distinct evidence of hepatocellular necrosis. However, in the SMB 500 mg/kg group, there was clear evidence of hepatocellular necrosis, characterized by the loss of cellular architecture and nuclear alterations. In the spleen photomicrographs (Figure 2), the control group displayed properly organized splenic architecture with identifiable trabeculae, white pulp, and red pulp. Conversely, the SMB 100 mg/kg and 300 mg/kg groups showed no discernible evidence of splenic injury. However, the SMB 500 mg/kg group demonstrated evidence of disrupted splenic architecture, including disruption of the splenic capsule, trabeculae, and red pulp.

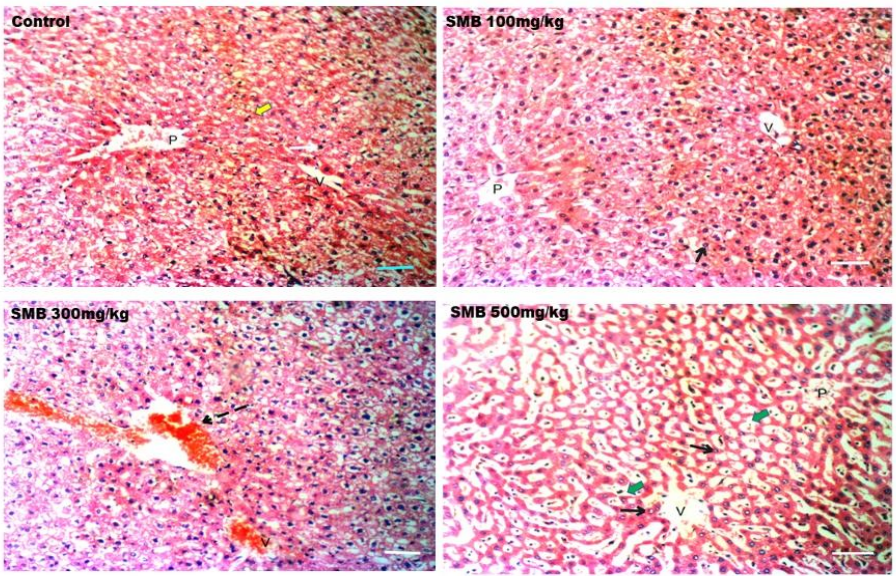

Fig. 1. Representative photomicrographs of rats' liver (H&E stain). The control group showed hepatocytes (black arrow) with normal sinusoids radiating from a central vein (V) toward the portal triad (P). The SMB 100 mg/kg and 300 mg/kg showed no clear evidence of hepatocellular necrosis. However, the SMB 500 mg/kg group showed evidence hepatocellular necrosis (green arrow) characterized by loss of cellular architecture and nuclear changes. SMB = sodium metabisulfite. Scale bar = 180 µm

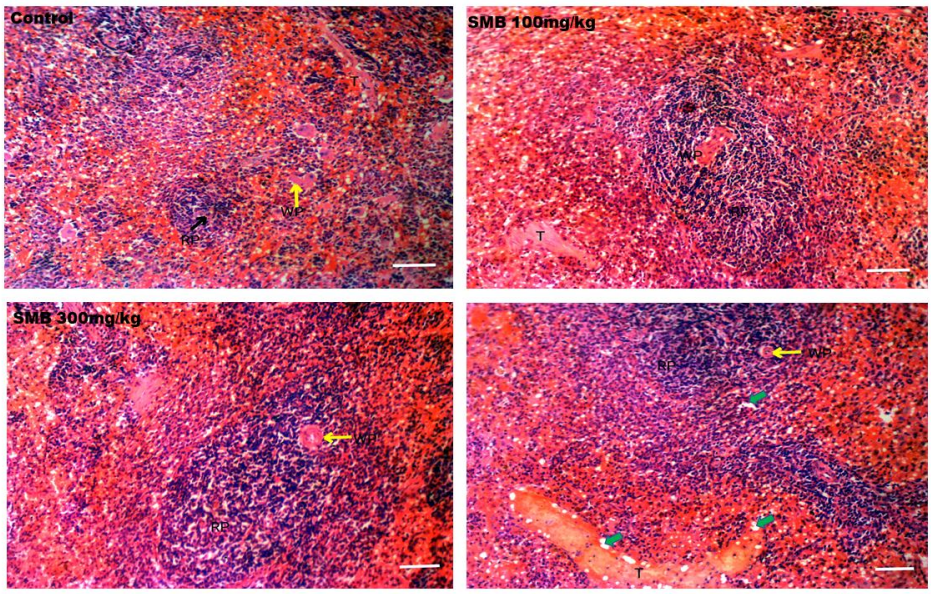

Fig. 2. Representative photomicrographs of rats' spleen (H&E stain). The control group shows properly arranged splenic architecture with distinct trabeculae (T), white pulp (WP) and red pulp (RP). The SMB 100 mg/kg and 300 mg/kg showed no clear evidence of splenic injury. The SMB 500 mg/kg group showed evidence of disruption of splenic architecture (green arow) characterized by disruption of the splenic capsule, trabeculae, and red pulp

Discussion

SMB has been found to have various adverse effects on blood and related parameters. Kadi et al. (5), reported that subchronic intake of SMB altered immune function, biochemical, hematological, and physiological parameters in Wistar rats. Shekarforoush et al. (4) found that SMB administration decreased serum antioxidant enzyme activities and increased lipid peroxidation in rats. Parker (19) demonstrated that bisulfite, a component of SMB, increased the passive permeability of RBC to sodium and potassium ions. This study shows that increasing doses of SMB led to a reduction in RBC count and platelet count. The decrease in RBC count and platelet count with increasing doses of SMB likely reflects its adverse effects on hematopoiesis, oxidative stress, and potential for immunological reactions or hemolytic events (4, 5). Also, this study shows that WBC and Hb levels are unaffected by the increasing doses of SMB. This finding suggests that within the parameters tested, SMB may have minimal impact on WBC and Hb levels, indicating potential safety within certain dosage ranges. However, further research is needed to fully elucidate its effects and ensure comprehensive safety assessments.

Aspartate and alanine aminotransferases play crucial roles in various metabolic processes. They are commonly used in the differential diagnosis of liver diseases. Increased levels of these enzymes indicate hepatocellular injury (20). This study shows that increasing doses of SMB result in increased levels of aspartate and alanine aminotransferases. The result suggests potential hepatotoxic effects of the substance at the doses administered, raising concerns about liver health and safety. Previous studies have reported that SMB has significant effects on the activities of aspartate and alanine aminotransferases, and ALP in human erythrocytes (21). These effects may be influenced by the presence of pyridoxal-5'-phosphate, a coenzyme that enhances the activities of these enzymes (22).

The liver's ALP is essential for the acute immune response in the liver, potentially aiding in mitigating inflammation and coagulation issues (23). This enzyme also holds clinical significance in diagnosing liver diseases, particularly hepatobiliary injuries (20). This study shows that increasing doses of SMB result in increased levels of ALP. The result suggests potential hepatobiliary injury due to the substance administered.

SMB has been found to have harmful structural and morphological effects on the liver (11). According to Naureen et al. (11), SMB (500 mg/kg bw) induces various defects in the liver like vacuolization, degeneration of hepatic cells and cell shrinkage, broad sinusoidal spacing, absence of bile canaliculus cells, regenerated Kupffer cells, and interrupted sheets of hepatocytes. Similar observations were seen in this study, with the addition of extensive evidence of hepatocellular necrosis (Figure 1), characterized by the loss of cellular architecture and nuclear alterations. This observation could be the reason the levels of aspartate and alanine aminotransferases, and ALP were all elevated in groups treated with SMB (particularly, 500mg/kg).

Research on the effects of SMB on the structure of the spleen is limited. However, a compound (sodium dodecyl sulfate) with similar properties to SMB was reported to have caused morphological changes in the spleen of gilthead fish (24). In this stud, the SMB 500mg/kg group showed disrupted splenic architecture, including disruption of the splenic capsule, trabeculae, and red pulp while other groups did not show distinct morphological changes. The splenic architectural disruption may indicate potential harmful effects of SMB on the spleen, potentially leading to compromised immune responses, blood filtration, and RBC recycling (25).

Conclusion

The administration of SMB at varying doses significantly impacted several hematological parameters and liver enzymes in rats. Specifically, the group administered SMB at 500mg/kg exhibited a significant decrease in RBC count and platelet levels compared to the control and lower-dose groups. Moreover, ALP levels, as well as alanine aminotransferase and aspartate aminotransferase levels, were significantly elevated in all SMB -treated groups compared to the control,

indicating potential liver damage. Histological analysis revealed hepatocellular necrosis in the group treated with 500mg/kg SMB, suggesting dose-dependent hepatotoxicity. Additionally, disruption of splenic architecture was observed in the group administered 500mg/kg SMB. These findings underscore the potential adverse effects of SMB on blood parameters, liver function, and splenic integrity, emphasizing the need for further investigation into its safety profile and appropriate dosing regimens.

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Ethical statement

The study protocol and treatment procedures were approved by the Research Ethics Committee of Adeleke University in Ede, Osun State, Nigeria (No: 00690) in agreement with the recommendations of the National Research Council Guidelines for Care and Use of Laboratory Animals (NRC Publication: 2011).

Data availability

None declared.

Conflict of interest

The authors declare no conflicts of interest with any entities.

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Author contributions

Nathaniel Ohiemi Amedu: participated in the design and interpretation of the study results, data analysis, and the review of the manuscript. Nathaniel Ohiemi Amedu, and Habeebullahi Abdur-Rahman: conducted the experiments, collected the tissue samples and contributed to the data analyses. Nathaniel Ohiemi Amedu and Habeebullahi Abdur-Rahman: performed histopathological, hematological and enzyme analyses. All authors participated in writing the drafts of the manuscript, and approved the final article prior to submission.

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