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Research Paper

Vitamin B Ameliorates Sodium Fluoride-Induced Oxidative Stress in Wistar Rats

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ABSTRACT

Background: Exposure to sodium fluoride (NaF) via sources such as the environment, use of toothpaste, and pesticides causes toxicity in the liver, kidneys, and brain, where it induces oxidative stress. Vitamin B plays an important role in the body by participating in metabolism and scavenging free radicals, thereby protecting the body against oxidative stress. Therefore, the present study aimed to determine the ameliorative effect of vitamin B on NaF-induced hepato-renal and brain damage.

Methods: A total of 20 adult male Wistar rats were used for the experiment. They were randomly divided into four groups of five rats each. G Group I was administered distilled water, Group II received NaF at 600 ppm, Group III received NaF at 600 ppm plus Vitamin B (10 ml/kg/day), and Group IV was administered Vitamin B (10 ml/kg/day) orally, daily for four weeks. Hematology, serum biochemical markers, and oxidative stress markers in the liver, kidneys, and brain were analyzed.

Results: The WBC, RBC, PCV, and hemoglobin were decreased in the NaF group. Moreover, serum ALT, AST, ALP, urea, and creatinine were significantly increased ($P<0.05$). There was a significant decrease ($P<0.05$) in catalase, glutathione peroxidase, and superoxide dismutase levels in the liver, kidneys, and brain. In addition, there was a significant increase ($P<0.05$) in liver, kidney, and brain malondialdehyde (MDA) in the NaF group compared to other groups.

Conclusion: The administration of Vitamin B alone did not cause any biochemical alterations in the liver, kidney, or brain. Co-administration of NaF and Vitamin B for four weeks ameliorated the oxidative changes induced by NaF in the liver, kidney, and brain.

Keywords: Biochemical changes, *In vivo* toxicity, Sodium fluoride (NaF), Vitamin B, Wistar rats, Oxidative stress

Introduction

Fluoride is ubiquitous in the environment and a valuable raw material in the agricultural and medical industries [1]. It is an essential trace element for soft tissue, body fluids, teeth, and bones [2]. However, chronic ingestion or inhalation of high sodium fluoride (NaF) doses causes adverse effects, such as bone diseases and non-skeletal fluorosis, in humans and animals [3,4,5]. Acute exposure to high levels of NaF causes severe tissue damage; on the other hand, exposure to minute quantities of fluoride results in delayed or impaired mineralization of bones and teeth since 95% of the ingested fluoride becomes deposited in them [6]. The kidneys are the major target of NaF toxicity because renal excretion of fluoride is one of the most important mechanisms regulating fluoride levels [7,8]. The NaF nephrotoxicity causes pathologic changes in the glomeruli as well as the proximal, distal, and collecting tubules of experimental animals [7,9,10]. The NaF salts induce oxidative stress, which produces free radicals that result in cell membrane damage and toxicity [7]. Exposure to NaF has been reported to reduce metabolic activities in the liver, such as glycolysis, oxidative phosphorylation, and lipid peroxidation. Furthermore, NaF increases serum indices of liver function [11]. Moreover, NaF significantly alters the cerebellar cortex's cellular arrangement, resulting in neurological abnormality and selective structural changes in the brain. Previous researches show that NaF causes toxicity by inducing oxidative stress by decreasing the levels of various

anti-oxidants like glutathione, superoxide dismutase, fat-soluble vitamins, and increased lipid peroxidation levels [7,12,13]. The use of vitamin B in this research is imperative as its antioxidant potential against NaF toxicosis remains largely unexplored. Due to their widely reported antioxidant benefits and relative affordability, it is necessary to explore the potential benefits of vitamin B against NaF-induced toxicity since humans and animals are exposed to NaF daily. The result of this study will add to the arsenal of antioxidants used against NaF toxicity.

Materials and Methods

Experimental Animals

A total of 20 male albino Wistar rats weighing between 150–170 g were purchased from Usmanu Danfodiyo University Teaching Hospital Sokoto (UDUTH) and kept at the animal house of the Department of Veterinary Pharmacology and Toxicology, Faculty of Veterinary Medicine Usmanu Danfodiyo University, Sokoto, Nigeria. The experimental animals were acclimatized (for 2 weeks) by housing in plastic cages (Five rats per cage) with access to water and standard pelleted feed ad libitum.

Chemicals

Commercial grade NaF (Guangdong Guangua Sci-Tech Chemical Co. Limited, China) was obtained from a reputable chemical Store in Zaria, Kaduna State, Nigeria. Vitamin B complex (Becombion® Nigeria, LTD) was purchased from a reputable pharmaceutical store in Sokoto.

Experimental Design

The experimental rats were randomly divided into four groups of five rats each as follows:

Group I: Control (distilled water only), Group II: Negative control Sodium fluoride (NaF at 600ppm), Group III: NAF (600ppm) + Vitamin B (NAFBCO) (10 ml/kg/day) 2020) Group IV: Vitamin B (10 ml/kg/day).

Oral daily treatment with NAF or Vitamin B (in normal saline) was done for four weeks (28 days), and weights were recorded. The animals were sacrificed at the end of the experiment (on the 28th day) following diethyl-ether anesthesia, and blood was collected.

Hematology and Biochemical Analysis

Blood samples were collected via the tail to determine hematological and biochemical parameters. Samples for hematological analysis were collected into anticoagulant sample bottles, while serum biochemistry samples were collected into clean phlebotomy tubes and allowed to clot. The clotted blood was centrifuged at 4,000 rpm for 10 min, and serum was collected into Eppendorf tubes and stored at -20ºC until use. From the collected serum sample, ALT, AST, ALP, urea, and creatinine were determined using Randox commercial kits.

Antioxidant Markers of Liver, Kidney, and Brain Samples

Fresh tissue samples from the liver, kidney, and brain tissue samples were homogenized in ice-cold saline using a glass homogenizer. Individually, each homogenate was centrifuged at 10,000 x g for 20 min, and the supernatant was collected for biochemical analysis.

The supernatant obtained from homogenization and centrifugation of liver, kidney, and brain samples were employed for the estimation of Catalase activity using the method presented in [14]. Glutathione peroxidase activity was determined as described in [15]. Superoxide dismutase was determined by measuring the inhibition of auto-oxidation of epinephrine at pH 10.2, as described in [16]. Moreover, the MDA level was calculated as described by [17].

Statistical Analysis

Data obtained from this experiment were expressed as Mean±SD and subjected to a one-way analysis of variance (One-Way ANOVA) along with Tukey's post hoc test for comparison. Statistical analysis was performed using GraphPad Prism (version 8.0). The P-value of 0.05 was considered significant.

Results

Effects of Subacute Oral Administration of BCO, NAF, and NAFBCO on Organ and Body/Weight Ratio of Organ

Exposure to NAF increased organ weight compared to BCO, control, and NAFBCO groups. There was a significant increase (P=0.0009) in the liver (g) and liver body weight (g/g) ratio of rats treated with NAF compared to control. There was no significant difference (P>0.05) in the kidney weight (g) and the kidney-to-body weight ratio of the control compared to those of the BCO, NAF, and NAFBCO groups (Table 1). There was no significant difference (P>005) in the brain weight and brain-body weight ratio between the control, BCO, NAF, and NAFBCO groups.

Effects of Subacute Oral Administration of BCO, NAF, and NAFBCO on Hematological Indices in Wistar Rats

Table 2 indicates the mean hematological indices of rats administered BCO, NAF, and NAFBCO. There was no significant difference (P>0.05) in the RBC and PCV between the control compared to the BCO, NAF, and NAFBCO groups. The WBC in the NAF group was significantly lower than the control group (P=0.0119). Although the WBC of the NAFBCO group was higher than that of NAF, there was no significant difference (P>0.05) between them. The Hb concentration was significantly lower (P=0.0008) in the NAF group compared to the control group. The percentage of

neutrophils and lymphocytes in the NAF group was significantly lower (P=0.0087 and P=0.0287, respectively) compared to that of the control group. (Table 2).

Table 1. Effect of Subacute oral administration of BCO, NAF, and NAFBCO on body, liver, and kidney weight in Wistar rats.

Parameter	Control	BCO	NAF	NAFBCO
Liver (g)	7.200±0.37[a]	7.400±0.41[a]	10.00±4.400[b]	7.40±0.62[b]
Liver/body weight (g/g)	0.045±0.003[a]	0.046±0.004[a]	0.054±0.003[b]	0.041±0.002[a]
Kidney (g)	0.950±0.38	0.98±0.04	1.16±0.23	1.02±0.02
Kidney/body weight(g/g)	0.0054±0.0002	0.0056±0.0003	0.017±0.025	0.007±0.0015
Brain Weight (g)	1.15±0.20	1.20±0.14	1.38±0.25	1.20±0.44
Brain Weight/Bodyweight (g/g)	0.006±0.004	0.005±0.0005	0.008±0.003	0.005±0.0005

Values with different superscripts (a,b) along each row differ (P<0.05).

Table 2. Effect of subacute oral administration of BCO, NAF, and NAFBCO on hematological parameters in Wistar rats.

PARAMETER	CONTROL	BCO	NAF	NAFBCO
WBC (10^3/µL)	13.5±1.30[a]	11.7±1.12[a]	7.35±1.80[b]	8.83±1.12[b]
RBC (10^6/µL)	7.48±0.47	7.93±0.93	6.08±0.30	6.67±0.16
Hb (g/dL)	13.4±0.34	13.76±0.58	8.97±1.31[a]	12.43±0.75
PCV (%)	42.00±1.73	43.00±2.65	35.67±1.86	37.19±1.82
Neutrophil (%)	35.00±4.36	25.33±3.71	16.3±3.48[a]	29.00±2.65
Lymphocytes (%)	80.0±7.20	67.30 ±5.13	60.70±7.57[a]	72.3±6.11
Monocytes (%)	3.00±0.57	3.00±1.00	1.67±0.33	2.33±0.67
Eosinophils (%)	2.00±1.00	1.67±0.88	0.33±0.33	0.67±0.57
Basophil (%)	ND	ND	ND	ND

Values with different superscript (a,b) along each row differ (P<0.05). ND: Not detected

Effects of Subacute Oral Administration of BCO, NAF, and NAFBCO on Serum Markers of Oxidative Stress

Serum catalase activity in the NAF group was significantly lower (P=0.0002) compared to the control group. However, there was no significant difference (P>0.05) between the control, BCO, and NAFBCO groups (Figure 1).

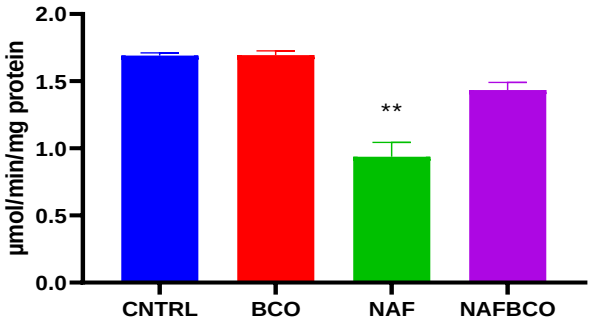

Figure 1. Effect of subacute oral administration of BCO, NAf and NAFBCO on serum catalase activity in Wistar rats.** significant difference at p<0.05.

Serum glutathione activity in the NAF group was significantly lower (P=0.0001) compared to the control group. Moreover, there was significant decrease (P=0.0018 and P=0.0001) between the BCO and NAFBCO groups compared to control (Figure 2).

Serum superoxide dismutase activity was significantly lower (P=0.0003 and P=0.0489) in the NAF and NAFBCO groups compared to the control group. There was no significant difference in the serum superoxide dismutase activity (P>0.05) between the BCO and control group (Figure 3).

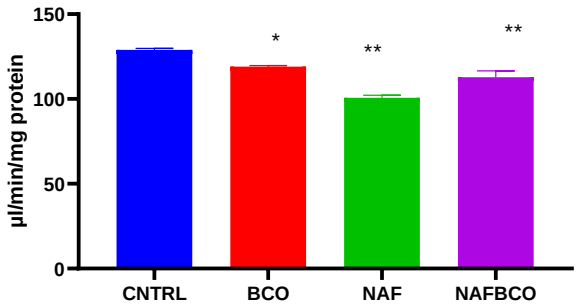

Figure 2. Effect of subacute oral administration of BCO, NAF, and NAFBCO on serum glutathione activity in Wistar rats. *,** significant difference at P<0.05

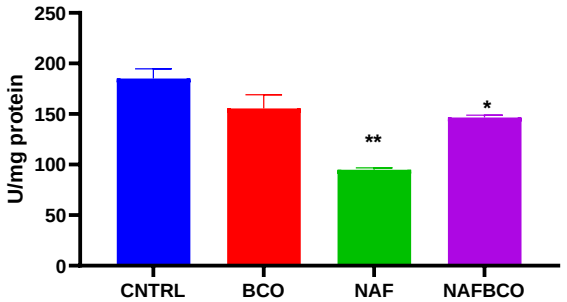

Figure 3. Effect of subacute oral administration of BCO, NAF, and NAFBCO on serum superoxide dismutase activity in Wistar rats. *,** significant difference at P<0.05.

Serum malondialdehyde (MDA) concentration was significantly higher (P<0.05) in the NAF and NAFBCO groups compared to the control group. There was no

significant difference (P>0.05) in the serum MDA between the BCO and control group (Figure 4).

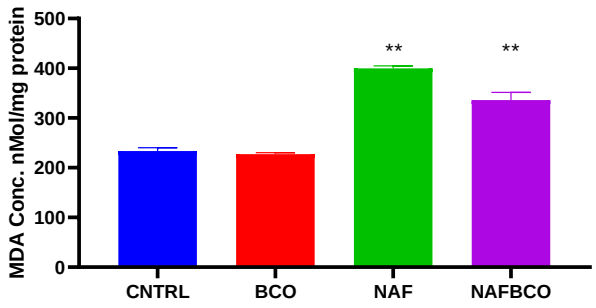

Figure 4. Effect of subacute oral administration of BCO, NAF, and NAFBCO on serum MDA activity in Wistar rats. ** significant difference at p<0.05

Effects of subacute oral Administration of BCO, NAF, and NAFBCO on Brain Markers of Oxidative Stress

There was no significant difference (P>0.05) in the brain catalase activity of the control compared to BCO, NAF, and NAFBCO groups (Figure 5).

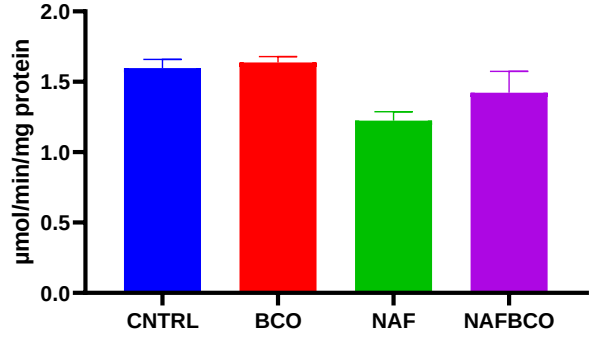

Figure 5. Effect of subacute oral administration of BCO, NAF, and NAFBCO on brain catalase activity in Wistar rats.

Brain glutathione activity was significantly lower (P=0.0011 and P=0.0208) in the NAF and NAFBCO groups compared to the control group. There was no significant difference (P>0.05) in the brain glutathione activity between the BCO and control group (Figure 6).

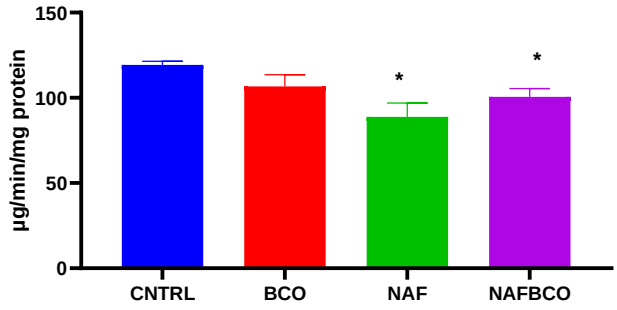

Figure 6. Effect of subacute oral administration of BCO, NAF, and NAFBCO on brain glutathione activity in Wistar rats. * significant difference at P<0.05

Brain MDA concentration was significantly higher (P<0.05) in the BCO, NAF, and NAFBCO groups (P=0.0099, P=0.0001, and P=0.0010, respectively) compared to the control (Figure 7).

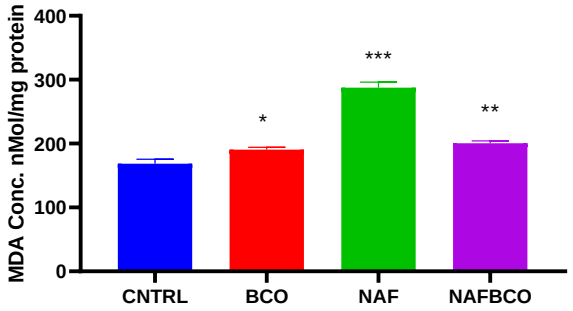

Figure 7. Effect of subacute oral administration of BCO, NAF, and NAFBCO on brain MDA concentration in Wistar rats. *,**,*** significant difference at P<0.05.

Brain superoxide dismutase activity was significantly lower (P=0.0496, P=0.0003, and P= 0.0026, respectively) in the BCO, NAF, and NAFBCO groups compared to the control group (Figure 8). The NAF group had the lowest brain superoxide dismutase activity.

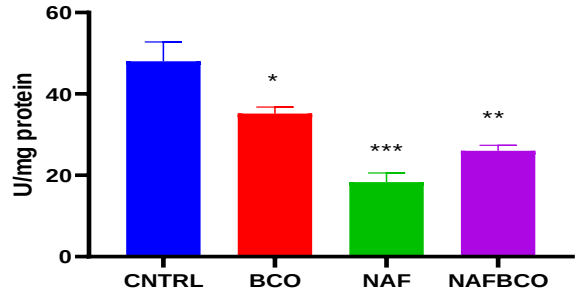

Figure 8. Effect of subacute oral administration of BCO, NAF, and NAFBCO on brain superoxide dismutase activity in Wistar rats. *, **,*** significant difference at P<0.05.

Serum Markers of Liver and Kidney Damage

Effects of Subacute Oral Administration of BCO, NAF, and NAFBCO On Serum Markers of Hepatic and Renal Damage in Wistar Rats

Table 3 revealed that markers of hepatic damage ALP and ALT were significantly higher (P=0.0001 and P=0.0037) in the NAF group compared to control. The AST was significantly higher (P=0.0001 and P=0.0006) in the NAF and NAFBCO compared to the control.

Urea concentration in the BCO, NAF, NAFBCO were significantly higher (P=0.008, P=0.0001, and P=0.0001, respectively) compared to control group. However, these values in the NAF group were the highest.

Creatinine concentration in the NAF group was significantly higher (P=0.0042) compared to control.

There was no significant difference in creatinine between the control, BCO, and NAFBCO.

Table 3. Effect of Subacute oral administration of BCO, NAF, and NAFBCO on Serum markers of renal and hepatic damage in Wistar Rats

PARAMETER	CONTROL	BCO	NAF	NAFBCO
ALP (U/L)	59.83±8.07[a]	70.11 ±14.31 [a]	167.2±13.55[b]	85.97±11.84[a]
AST (U/L)	57.29±4.68[a]	74.62±7.12[a]	111.6±6 .08[b]	96.27±7.94[b]
ALT (U/L)	17.43±0.95[a]	17.99±2.94[a]	21.46±3.58[b]	19.2± 1.60[a]
Urea (mmol/l)	10.78±0.71[a]	13.9±1.34[b]	22.38±1.49[b]	16.67±0.59[b]
Creatinine (mmol/l)	14.56±1.11[a]	15.5±0.23[a]	17.81±1.82[b]	16.15±0.94[a]

Values with different superscripts (a,b) along each row differ (P<0.05).

Effects of Subacute Oral Administration of BCO, NAF, and NAFBCO on Kidney Markers of Oxidative Stress in Wistar Rats

Kidney catalase activity was significantly lower (P=0.0009 and P=0.0066) in the NAF and NAFBCO groups compared to the control group. There was no significant difference in the kidney catalase activity (P>0.05) between the BCO and control group (Figure 9).

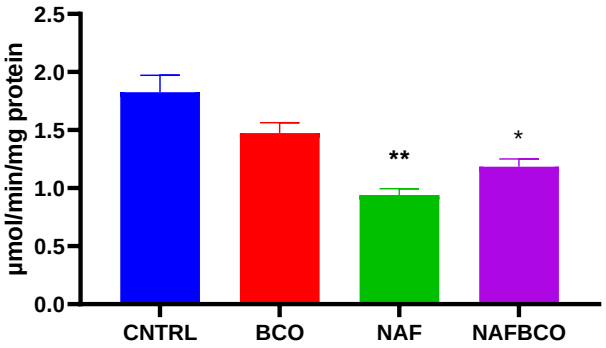

Figure 9. Effect of subacute oral administration of BCO, NAF, and NAFBCO on kidney catalase activity in Wistar rats. *, ** significant difference at P<0.05.

Kidney MDA concentration was significantly higher (P<0.05) in the BCO, NAF, and NAFBCO compared to control (Figure 10).

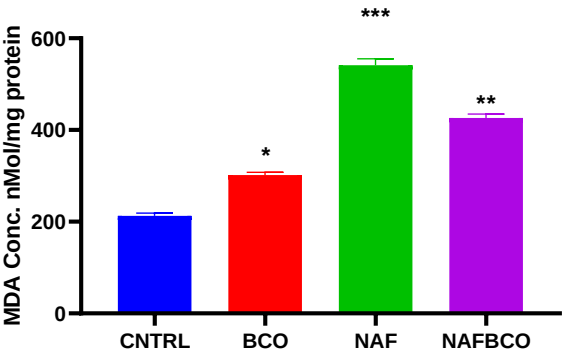

Figure 10. Effect of subacute oral administration of BCO, NAF, and NAFBCO on kidney MDA concentration in Wistar rats. *, **, *** significant difference at P<0.05.

Kidney glutathione peroxidase activity is significantly lower (P=0.0001 and P=0.0021) in the NAF and NAFBCO groups compared to the control group (Figure 11).

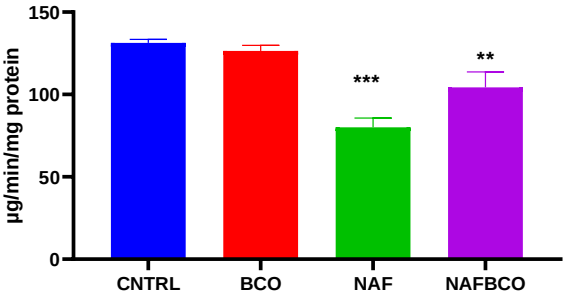

Figure 11. Effect of subacute oral administration of BCO, NAF, and NAFBCO on kidney glutathione peroxidase activity in Wistar rats. **,*** significant difference at P<0.05.

Results interpreted from Figure 12 demonstrated that the kidney superoxide dismutase activity was significantly lower in the BCO, NAF, and NAFBCO groups (P=0.0019, P=0.0001, and P=0.0001, respectively) compared to the control group.

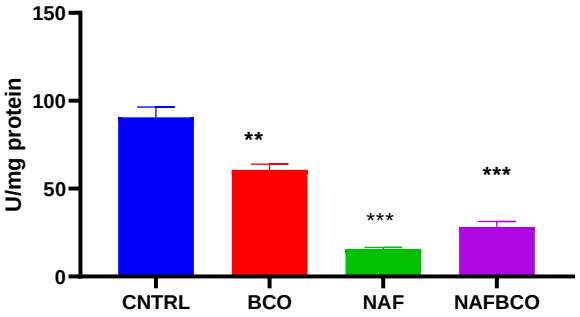

Figure 12. Effect of subacute oral administration of BCO, NAF and NAFBCO on kidney superoxide dismutase activity in Wistar rats. **,***significant difference at p<0.05

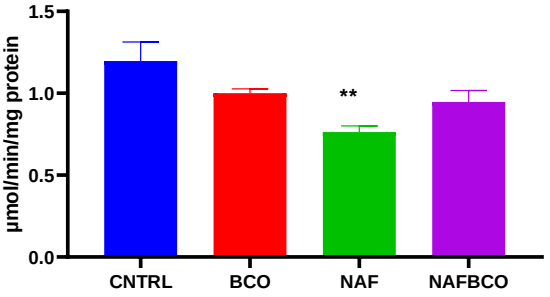

Figure 13. Effect of acute oral administration of BCO, NAF, and NAFBCO on liver catalase activity in Wistar rats. ** significant difference at P<0.05.

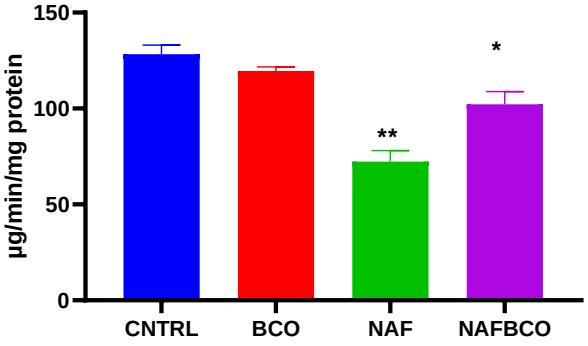

Figure 14. Effect of subacute oral administration of BCO, NAF, and NAFBCO on liver glutathione peroxidase activity in Wistar rats. *, ** significant difference at P<0.05.

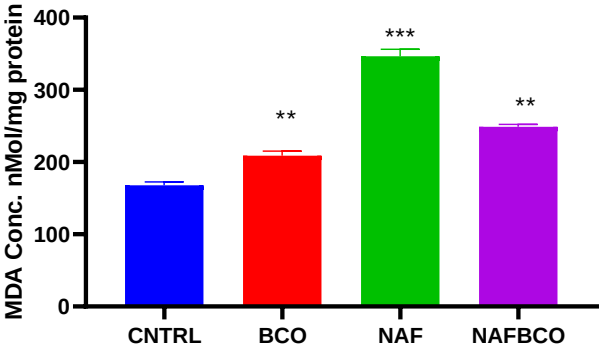

Figure 15. Effect of Subacute oral administration of BCO, NAF, and NAFBCO on liver MDA concentration in Wistar rats. *, ** significant difference at P<0.05.

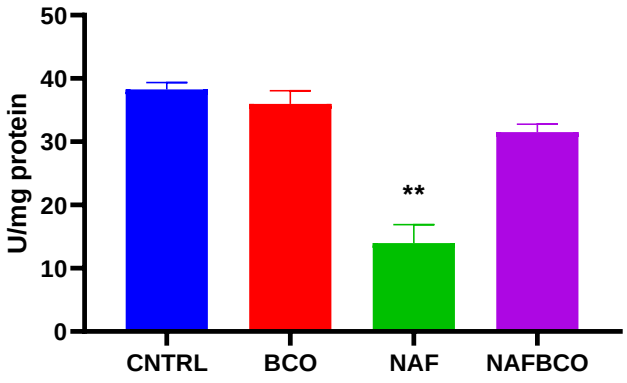

Figure 16. Effect of Subacute oral administration of BCO, NAF, and NAFBCO on liver superoxide dismutase activity in Wistar rats. ** significant difference at P<0.05.

The results of the effect of BCO, NAF and NAFBCO on liver markers of oxidative stress are shown in Figures 13-16. The liver catalase activity was significantly lower (P = 0.0115) in the NAF group compared to the control. There was no significant difference in the BCO and NAFBCO liver catalase activity compared to the control (Figure 13). Furthermore, the liver glutathione peroxidase activity was significanficantly lower (P= 0.0001 and P = 0.0010) in the NAF and NAFBCO groups compared to the control group (Figure 14).

The liver malondialdehyde concentration was significantly higher (P = 0.003, 0.0001 and 0.001, respectively) in the BCO, NAF and NAFBCO groups compared to the control (Figure 15). The liver superoxide dismutase activity was significantly lower (P = 0.0001) in the NAF group compared to the control (Figure 16).

Discussion

Many studies have established the relationship between liver and kidney damage with NaF exposure in rats [7, 18].

The liver-to-body and kidney-to-body weight ratios provide additional information on the absolute liver or kidney weight data reflecting the effect of NaF and vitamin B in changes in their weights. The increase in liver and kidney weight seen in the NaF-treated group (Table 1) may be a result of hepatocellular hypertrophy due to enzyme induction or peroxisome proliferation following exposure to a toxicant [19,20]. The increased brain-to-body weight ratio in the NAF group seen in this study may be due to the relative permeability of the blood-brain barrier to fluoride [21]. Although changes in brain weight are rarely associated with neurotoxicity [19], high fluoride exposure in rats may cause mild brain cell damage without functional changes [21].

The decrease in the body weight of these organs of the Vitamin B and NAFBCO groups may be because vitamin B has been documented to reduce body weight gain by improving energy metabolism-related enzyme activities such as glucose-6-phosphate dehydrogenase, pyruvic acid kinase, and succinate dehydrogenase [22].

The present study indicates a correlation between NAF administration and blood parameters. The treatment of Wistar rats with NAF alone demonstrated a significant decrease in WBCs, RBC, Hb, PCV, neutrophils, lymphocytes, and monocytes. This is in line with the results of [23]. The decrease may be attributed to the inhibitory effect of NaF on the hematopoietic system [23]. Furthermore, fluorides damage RBCs and cause the formation of echinocytes. The damaged echinocytes are removed via phagocytosis, which results in a decrease in Hb and RBC [24]. The improvement following vitamin B administration showed that vitamin B ameliorated the harmful effects of NaF in the hematopoietic system. The decrease in WBC in the NaF-treated group is in agreement with [25] and may be due to oxidative stress and modification of cellular membrane lipids. The improvement in WBC in the Vitamin B and NaF + Vitamin B groups may be because of the direct scavenging of reactive oxygen species by Vitamin B [26]. Serum markers of oxidative stress showed significant changes. The catalase, superoxide dismutase, and glutathione peroxidase activities in the serum decreased significantly, while the MDA increased significantly following exposure to NaF. It is known that NaF is associated with oxidative stress. Increased generation of reactive oxygen species (free radicals) by NaF caused the reduction in the cellular antioxidant concentration, and this is responsible for

the reduced concentration of catalase, superoxide dismutase, and glutathione peroxidase activities seen in the NAF group in agreement with [27]. Furthermore, the increased MDA concentration in the NAF-treated group may result from membrane lipid peroxidation, as reported by [12]. The MDA is a reliable marker of oxidative stress-mediated lipid peroxidation in tissues [28]. Exposure to fluoride produces free radicals and reactive species, which leads to redox imbalance. This has been suggested to be the major mechanism of action for fluoride toxicity [12,27]. The reduction in the NAFBCO group suggests that treatment with Vitamin B ameliorates oxidative stress induced by NAF.

In the present study, a significant decrease was observed in the catalase, glutathione peroxidase, and superoxide dismutase activity of the brain in the NAF-treated Wistar rats. This decrease may be because this endogenous antioxidant plays a significant role in scavenging free radicals induced by NAF administration. The increase in the catalase, glutathione peroxidase, and superoxide dismutase activity in the BCO and NAFBCO group suggests that treatment with Vitamin B ameliorates oxidative stress induced by NAF.

Furthermore, the present work showed significant changes in the activities of serum markers of liver and kidney damage. It has been earlier reported that these enzymes are reliable biomarkers and prognostic determinants for liver and kidney tissue damage caused by NaF [7]. As reported in earlier studies, the increase in AST, ALT and ALP enzymes in the NAF group may be due to liver damage [12,24]. Damage to the liver caused some of these enzymes to lseak into the serum, which elevated values in this group. The amelioration by Vitamin B, which caused a reduction in AST, ALT, and ALP in both the BCO and NAFBCO groups, could be due to the indirect stimulation of reactive oxygen scavenging by the preservation of antioxidants, such as glutathione in the system [27]. Moreover, urea and creatinine showed a significant increase, which may result from increased protein catabolism resulting from NaF-induced systemic oxidative damage, as reported by [12]. Increased urea and creatinine in the NAF group suggests extensive glomerular damage, which may also reduce the clearance rate from the kidneys, and therefore, its increase in blood circulation [12]. Lipid peroxidation, the primary measure of oxidative damage, is a chain of reactions in which lipids are degraded. MDA is the index of lipid peroxidation. MDA is a reliable marker of oxidative stress-mediated lipid peroxidation in tissues [28]. The present study also revealed significant changes in the MDA concentrations of the liver and kidney compared to those of the control, BCO, and NAFBCO groups. The increased MDA seen in this study is in line with the findings of [28]. The increased MDA in the liver and kidney in this study indicates increased lipid peroxidation in these organs, increasing oxidative damage. Increased peroxidation of membrane lipids is a significant sequelae of oxidative damage produced by NAF in rats [28, 29]. The reduction in the NAFBCO group suggests that treatment with Vitamin B ameliorates oxidative stress induced by NAF.

In the present study, a significant decrease was observed in the catalase, glutathione peroxidase, and superoxide dismutase activity of the liver and kidney of the NAF-treated Wistar rats. This decrease may be because these endogenous antioxidants played a significant role in trying to scavenge free radicals induced by NAF administration. The increase in the catalase, glutathione peroxidase, and superoxide dismutase activity in the BCO and NAFBCO group suggests that treatment with Vitamin B ameliorates oxidative stress induced by NAF.

Conclusions

The present study revealed the hepato-renal and brain protective potentials of Vitamin B in NAF-induced oxidative stress in Wistar rats.

Conflict of Interests

The authors declare that there is no conflict of interest to disclose.

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Compliance with Ethical Guidelines

The animal experiments in the present work were approved by the Institutional Animal Care and Use Committee of the Usmanu Danfodiyo University, Sokoto (UDUS/IACUC/2022/AUR-RO-O3).

Authors' Contributions

Idris SB and Onimisi BO designed and conceptualized the idea. Yusuf SM and Shafiu U, under supervision, collected the data. Idris SB, Onimisi BO, and Fasuyi FH conducted the data analysis and manuscript drafting.

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