**RESEARCH**

# Sodium Pentaborate Prevents Acetaminophen-Induced Hepatorenal Injury by Suppressing Oxidative Stress, Lipid Peroxidation, Apoptosis, and Inflammatory Cytokines in Rats

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## Abstract

Acetaminophen (N-acetyl-p-aminophenol, APAP, or paracetamol) is one of the drugs that may be damaging to the kidneys and liver when used in excess. In this context, it is vital to treat these side effects on the liver and kidneys with various antioxidants. Diseases have been treated using herbal and mineral remedies since ancient times. The mineral boron, found in rocks and water, is a crucial ingredient with multiple positive biological effects. The primary objective of this research is to determine whether or not boron has a protective effect against the toxicity generated by APAP in rats. Male Sprague-Dawley rats were pretreated orally with boron-source sodium pentaborate (B50 and B100 mg/kg) for 6 days by gastric gavage in order to counteract the toxicity caused by a single dose of APAP (1g/kg). APAP increased lipid peroxidation as well as serum BUN, creatinine concentrations, and serum activities of AST, ALP, and ALT by consuming GSH in liver and kidney tissues. In addition, the activity of antioxidative enzymes, including SOD, CAT, and GPx, was diminished. Inflammatory indicators such as TNF-α, IL-1β, and IL-33 were elevated in conjunction with APAP toxicity. In kidney and liver tissues, APAP dramatically increased the activity of caspase-3 and triggered apoptosis. Sodium pentaborate therapy on a short-term basis reduced biochemical levels despite these effects of APAP. This study showed that boron protects rats from the harmful effects of APAP by acting as an anti-inflammatory, antioxidant, and anti-apoptotic agent.

**Keywords** Acetaminophen · Sodium pentaborate · Lipid peroxidation · Oxidative stress · Inflammation · Apoptosis

## Introduction

Numerous vital physiological tasks, including detoxification, glucose regulation, cholesterol synthesis, and coagulation factor production, are performed by the liver. Even though the liver may regenerate, significant damage can result in liver failure and even death [1]. Kidneys take part in essential processes such as homeostasis, regulation of water, acid-base and electrolyte balance, endocrine functions, and excretion. It is stated that various toxic effects increase the sensitivity of nephrons, making their physiological and biochemical qualities far more sensitive to toxic damage than those of other organs [2]. Due to the heterogeneity of nephrons, some kidney regions are more responsive than others. Nearby nephrons contain significantly more carrier systems. Particularly the liver and kidney are organ targets for several toxic metabolites and are exposed to greater toxicity due to crucial metabolic events (associated with GSH) [3]. When used on a regular basis, acetaminophen, aspirin, ibuprofen, naproxen, indomethacin, and COX-2 inhibitors have been known to trigger harm to the kidneys, liver, and perhaps other organs in the body [4].

The medicine APAP is considered safe enough to use on youngsters, but long-term usage can be harmful to the kidneys and liver. Numerous investigations have found that chronic APAP usage causes damage to the kidneys and liver [5–7]. APAP undergoes substantial and moderate glucuronidation, sulfation, and microsomal oxidation (cytochrome

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p450) reactions during metabolic metabolism [8]. APAP's poisonous metabolite, N-acetyl p-benzokinoimine (NAPQI), is quickly eliminated in the urine by interacting with reduced glutathione during the cytochrome p450 system step (GSH). However, when APAP is taken in excess, glutathione is depleted, and the body cannot eliminate the built-up NAPQI. Toxic effects are caused by the NAPQI metabolite's covalent binding to proteins, lipids, DNA, and other crucial macromolecules [6, 9]. As a consequence of this, the hypothesis that reactive oxygen species are released in the cell, which leads to toxicity, has been supported by several studies [10, 11]. Efforts have been undertaken in recent years to create various therapeutic therapies for such poisonings. In the realm of alternative medicine, herbal medicine and minerals are of particular interest to scientists. They perform study on the paths and processes through which these medications exert their effects. Since antiquity, boron and its derivatives have been utilized in several disciplines of medicine and industry. Recent applications in the realm of health have led to promising research [12].

Boron, an essential bioelement, is recognized to play an important role in all living creatures' fundamental processes [13]. Boron is known to have two significant functions in the body, the first of which is a hormonal response to transmembrane signaling and the movement of regulatory ions in the cell membrane structure [14]. It also serves as an enzymatic regulator in metabolism [15]. Boron and its derivatives have been shown in studies to have beneficial impacts on minerals, hormones, vitamins, enzymes, and cytokines [16–19]. As a result, it can help with arthritis [20], osteoporosis [21], tooth-bone [22], stroke [12], diabetes [23], heart [24], brain [25] aging [26], immunity [27], and obesity [28]. It is stressed that it increases antioxidant defenses by avoiding lipid peroxidation and heavy metal-induced DNA and genotoxic damage [29, 30]. Furthermore, boron and its compounds have anti-inflammatory and antibacterial properties [19, 31, 32]. A recent study on persons exposed to boron minerals through their environment found that oxidative stress and inflammatory parameters in blood levels did not rise [33]. In this work, APAP generated oxidative stress in rat kidney and liver tissues, and the capacity of sodium pentaborate to protect against tissue damage was studied using multiple biochemical parameters.

## Material and Methods

### Drugs and Chemicals

In this study, Parol pills (500 mg per tablet; Atabay Chemical Industry, Istanbul, Türkiye) were employed as a source of APAP (paracetamol). One gram per kilogram of APAP was supplied orally as a single dosage. Literature-based data indicate that APAP is typically administered in high concentrations and as a single dose [34–36].

The sodium pentaborate ($NaB_5O_8 \cdot 5H_2O$) compound was supplied commercially by a manufacturer (Kale Natural Company, Balıkesir, Türkiye). Rats were administered oral doses of 50 and 100 mg/kg diluted in distilled water for 6 days [30, 37].

Short-term oral treatment of 100 mg/kg of boron compounds is nontoxic to animals, and the reported fatal dosage for laboratory animals (mice-rat) is 400–700 mg/kg [38, 39]. At physiological pH, inorganic borates are reportedly converted to boric acid, absorbed from mucosal surfaces, and more than 90% of them are eliminated as boric acid in the urine [40].

### Animals

The 35 Sprague-Dawley male rats weighing 250–300 g utilized in the study were procured from the Ataturk University Medical Experimental Research and Application Center. Furthermore, this study looked into the effects of the medicine and antioxidant chemical on a certain biological process in rats. Since hormonal fluctuations in female rats may change the analysis results, only male rats were preferred instead of female rats.

The rats were divided into five groups, seven of which were weighed without any statistical difference between the groups. The animals were confined to cages with a constant temperature of 24 to 25°C and a 12-h dark-light cycle. The rats were acclimated to their habitat for 1 week before the experiment and were supplied standard pellet food and water ad libitum during the trial. In Table 1, the standard pellet feed content of the institution is given. In addition to this table, the list of ingredients includes trace amounts of corn, soybean meal, corn gluten, sugar beet molasses, dicalcium phosphate, calcium carbonate, sodium chloride, sodium bicarbonate, and other vitamins and minerals.

**Table 1** Ataturk University Medical Experimental Research and Application Center's standard pellet feed content in rat diet

| Ingredients | Standard | Unit |
| --- | --- | --- |
| Crude protein | 23.00 | % |
| Crude lipid | 1.70 | % |
| Crude cellulose | 3.70 | % |
| Sodium | 0.60 | % |
| Vitamin A | $12 \times 10^6$ | IU/kg |
| Manganese | 95 | mg/kg |
| Iron | 31 | mg/kg |
| Zinc | 96 | mg/kg |
| Cobalt | 0.50 | mg/kg |
| Selenium | 0.30 | mg/kg |
| Iodine | 2.28 | mg/kg |

Ataturk University Animal Experiments Local Ethics Committee accepted the procedure for the animals used in the experiment (Approval No: 2017-7/104).

## Experimental Design

In this study, rats were divided into 5 groups, each of which was divided into 7 groups, and were administered for 6 days as indicated as follows:

- Control group: A physiological serum was administered orally for only 6 days.
- APAP (acetaminophen): Six days of oral saline were given, and on the sixth day, 30 min after saline application, a single dose of 1 g/kg oral APAP was given to provide toxicity.
- B100 (Sodium pentaborate, 100 mg/kg): Sodium pentaborate was given orally for 6 days.
- APAP+B50 (acetaminophen + sodium pentaborate): Sodium pentaborate was given orally (50 mg/kg/day) for 6 days, and a single dose of APAP (1 g/kg) was given 30 min after sodium pentaborate administration on day 6.
- APAP+B100 (acetaminophen + sodium pentaborate): Sodium pentaborate was given orally (100 mg/kg/day) for 6 days, and a single dose of APAP (1 g/kg) was given 30 min after sodium pentaborate administration on day 6.

At the end of the study (24 h after APAP administration, seventh day), animals were decapitated under sevoflurane (sevorane liquid 100%, Abbott Laboratory, Istanbul, Türkiye) anesthesia, and blood, tissue, and liver samples were taken.

## Sample Collection

Blood samples were transferred to anti-coagulant-free tubes for biochemical analysis. Serum was separated by centrifugation at $1000 \times g$ for 10 min at +4°C and kept at −20°C until analysis. Rats' tissue was taken and stored at −20°C until biochemical experiments were performed.

## Renal and Liver Function Analysis

Serum blood urea nitrogen (BUN), creatinine levels, aspartate aminotransferase (AST), alkaline phosphatase (ALP), and alanine aminotransferase (ALT) activities were measured using commercial kits (YL Biont, Shanghai, China, sandwich enzyme-linked immunosorbent assay).

## Analysis of Oxidants and Antioxidants

In this study, tissue superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) activities and malondialdehyde (MDA) and glutathione (GSH) levels were analyzed by ELISA kits (YLBiont, Shangai, China, sandwich enzyme-linked immunosorbent assay).

## Assay of Inflammation

Tissue tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β), and interleukin-33 (IL-33) levels were measured using ELISA kits (YLBiont, Shanghai, China brand sandwich enzyme-linked immunosorbent assay).

## Assay of Apoptosis

Tissue cysteine aspartate specific protease-3 (caspase-3) activity was measured using kit instructions (YLBiont, Shangai, China sandwich enzyme-linked immunosorbent assay).

## Statistical Analysis

The statistical analysis of this study was performed using the SPSS 20.0 software program. Statistical differences and significance levels in all measurements were determined by the one-way analysis of variance (ANOVA) test, and the Tukey test was applied to multiple comparisons. All values were given as mean ± standard deviation (SD). Results of $p < 0.05$ were considered significant.

## Results

### Serum Renal and Liver Function Analysis

Serum BUN and creatinine levels both rose (Table 2) in the APAP group compared to the control group ($p<0.05$). There was no statistically significant difference between the control and B100 groups ($p> 0.05$). While APAP treatment significantly elevated serum BUN and creatinine levels ($p <0.05$), it was revealed that these values were reduced ($p <0.05$) in the groups in which sodium pentaborate was treated in addition to APAP (APAP+B50, APAP+B100). It is revealed in Table 3 that serum AST, ALT, and ALP enzyme activities, which are known as liver function tests, are enhanced in the APAP group compared to the control group ($p<0.05$). Furthermore, it was observed that enzyme activity in APAP+B50 and

**Table 2** Effect of sodium pentaborate on serum BUN, creatinine levels, and kidney tissue MDA, SOD, GSH, GPx, and CAT activities/levels in toxicity of APAP

| Parameter | Control | APAP | B100 | APAP+B50 | APAP+B100 |
|---|---|---|---|---|---|
| BUN (mmol/L) | $2.22\pm0.05^d$ | $4.45\pm0.09^a$ | $2.05\pm0.06^d$ | $3.54\pm0.08^b$ | $2.98\pm0.07^c$ |
| Creatinine (μmol/L) | $40.85\pm0.79^d$ | $75.33\pm0.92^a$ | $39.44\pm0.77^d$ | $65.48\pm0.85^b$ | $48.75\pm0.81^c$ |
| MDA (nmol/g tissue) | $17.84\pm0.21^d$ | $27.09\pm0.58^a$ | $16.65\pm0.34^d$ | $23.77\pm0.33^b$ | $20.65\pm0.34^c$ |
| SOD (ng/mg protein) | $0.35\pm0.03^a$ | $0.14\pm0.01^d$ | $0.37\pm0.02^a$ | $0.22\pm0.03^c$ | $0.28\pm0.03^b$ |
| CAT (ng/g protein) | $3.81\pm0.09^a$ | $1.93\pm0.04^d$ | $3.99\pm0.06^a$ | $2.42\pm0.07^c$ | $2.93\pm0.06^b$ |
| GSH (nmol/g tissue) | $10.52\pm0.27^a$ | $5.05\pm0.11^d$ | $10.74\pm0.42^a$ | $6.18\pm0.16^c$ | $7.91\pm0.21^b$ |
| GPx (ng/g protein) | $3.23\pm0.06^a$ | $1.31\pm0.05^d$ | $3.32\pm0.06^a$ | $1.92\pm0.05^c$ | $2.71\pm0.06^b$ |

The different superscripts (a–d) shown on the same line indicate a significant difference ($p<0.05$) between the groups

**Table 3** Effect of sodium pentaborate on serum AST, ALT, and ALP activities and liver tissue MDA, SOD, GSH, GPx, and CAT activities/levels in toxicity of APAP

| Parameter | Control | APAP | B100 | APAP+B50 | APAP+B100 |
|---|---|---|---|---|---|
| AST (U/L) | $49.78\pm0.68^d$ | $95.46\pm2.15^a$ | $54.24\pm0.98^d$ | $74.13\pm1.15^b$ | $64.62\pm1.11^c$ |
| ALT (U/L) | $42.36\pm0.71^d$ | $80.36\pm1.21^a$ | $42.73\pm0.59^d$ | $67.54\pm1.36^b$ | $58.43\pm0.79^c$ |
| ALP (U/L) | $57.09\pm1.34^d$ | $107.57\pm2.88^a$ | $59.33\pm1.31^d$ | $88.09\pm1.55^b$ | $73.05\pm1.08^c$ |
| MDA (nmol/g tissue) | $12.73\pm0.35^d$ | $20.79\pm0.55^a$ | $11.79\pm0.32^d$ | $18.04\pm0.21^b$ | $15.56\pm0.29^c$ |
| SOD (ng/mg protein) | $0.51\pm0.01^a$ | $0.28\pm0.01^d$ | $0.53\pm0.01^a$ | $0.36\pm0.01^c$ | $0.42\pm0.01^b$ |
| CAT (ng/g protein) | $2.91\pm0.09^b$ | $1.75\pm0.07^d$ | $3.49\pm0.07^a$ | $2.07\pm0.04^c$ | $2.25\pm0.05^c$ |
| GSH (nmol/g tissue) | $8.94\pm0.35^a$ | $4.19\pm0.22^d$ | $8.91\pm0.18^a$ | $5.38\pm0.14^c$ | $7.13\pm0.24^b$ |
| GPx (ng/g protein) | $2.45\pm0.03^a$ | $1.21\pm0.05^d$ | $2.51\pm0.03^a$ | $1.54\pm0.02^c$ | $2.02\pm0.04^b$ |

The different superscripts (a–d) shown on the same line indicate a significant difference ($p<0.05$) between the groups

APAP+B100 groups reduced compared to the APAP group ($p<0.05$), bringing them closer to the control group values.

## Lipid Peroxidation

Examination of kidney MDA levels revealed that APAP treatment increased kidney MDA levels compared to the control group ($p<0.05$). Evaluating kidney MDA levels, it was encountered that APAP application raised kidney MDA levels relative to the control group, as indicated in Table 2 ($p<0.05$). It was determined that B50 and B100 dosages applied in conjunction with APAP reduced this level ($p<0.05$). B100 dosage was shown to be more effective than the B50 dose in reducing kidney MDA levels (Table 2). It was revealed that the level of MDA in liver tissue increased considerably in the paracetamol group compared to the control group and reduced significantly ($p<0.05$) in both sodium pentaborate dosages (APAP+B50, APAP+B100, Table 3).

## Antioxidant Enzymes and Reduced GSH

SOD, CAT, and GPx antioxidant enzyme activities and GSH levels decreased ($p<0.05$) in the APAP group compared to the control group. On the other hand, it was shown that both sodium pentaborate dosages (B50 and B100), but notably the B100 dose, significantly boosted antioxidant enzyme activities and GSH levels in kidney tissue ($p<0.05$, Table 2). In addition, it was established that both pre-treatment dosages of sodium pentaborate, notably in the APAP+B100 group, significantly improved antioxidant enzyme activities and GSH levels in liver tissue ($p<0.05$, Table 3). There was no statistically significant difference between the APAP+B50 and APAP+B100 groups regarding liver CAT activity ($p>0.05$).

## Analysis of Inflammatory Cytokines

There was no statistical difference between the TNF-α levels of the control and B100 groups in this investigation ($p>0.05$). APAP substantially raised kidney TNF-α levels relative to the control and B100 groups ($p<0.05$), but APAP + B50 and APAP + B100 dose-dependently lowered these levels (Fig. 1, $p<0.05$).

There was no statistically significant difference between the levels of IL-1β in renal tissue between the control and B100 groups (Fig. 1, $p>0.05$). In the APAP group, where nephrotoxicity was observed, the level of IL-1β was higher than that in the control group ($p<0.05$). Compared to the APAP group, the higher IL-1β levels in the APAP+B50 and APAP+B100 groups were reduced with increasing dosage ($p<0.05$).
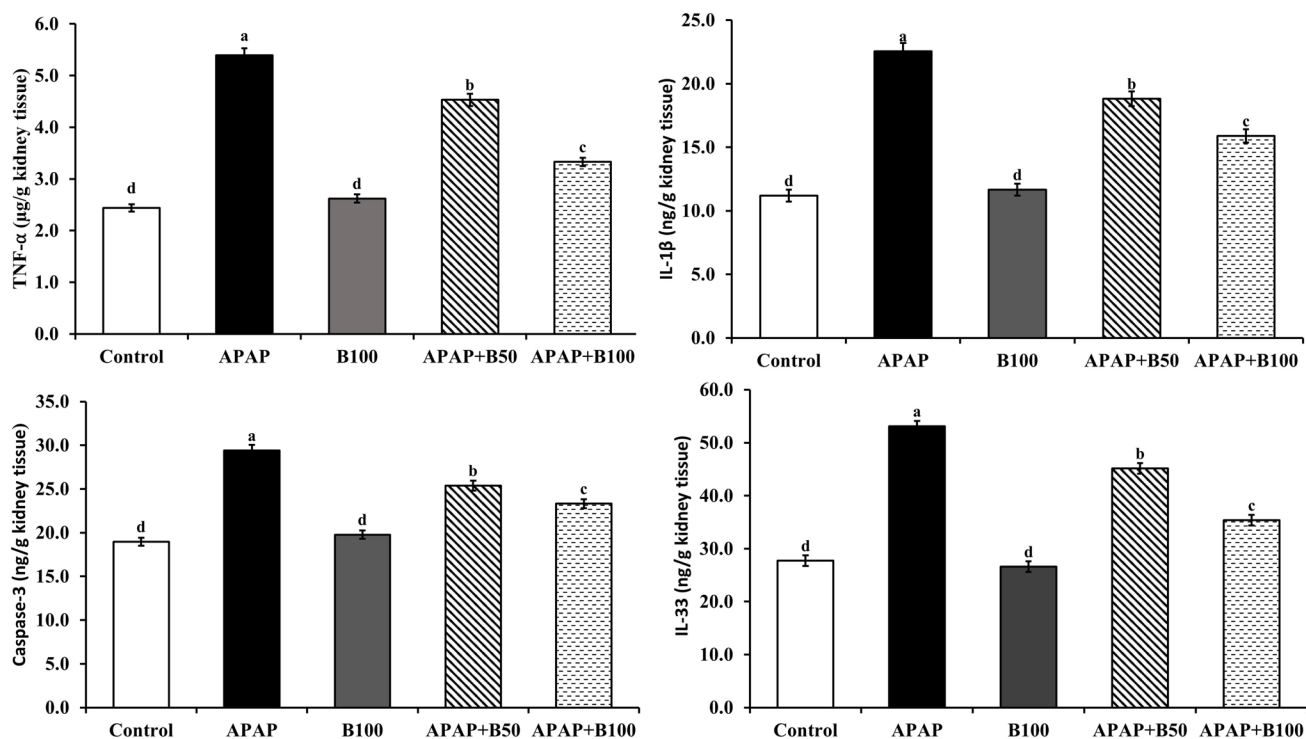
**Fig. 1** Effect of sodium pentaborate and APAP on TNF-α, IL-1β, IL-33, and caspase-3 in rat kidney tissue. Data represent the means ± SD of seven rats in each group. Results were derived from one-way ANOVA followed by Tukey's post hoc test. **a–d** Significant (*p*<0.05) differences among groups

It was established that there was no statistically significant difference between the control and B100 groups in the level of IL-33, a particular marker for kidney tissue (*p*>0.05). The APAP-treated groups had greater IL-33 levels than the control and B100 groups (*p*<0.05). The elevated IL-33 levels in the APAP+B50 and APAP+B100 groups dropped considerably relative to the APAP group (*p*<0.05). B100 dosage was found to lower IL-33 levels more effectively than the B50 dose (Fig. 1).

The liver TNF-α and IL-1β levels after APAP administration did not differ significantly between the control and B100 groups (*p*>0.05), although there was a substantial rise in cytokine levels in the paracetamol-treated group (*p*>0.05). In addition, reductions (*p*<0.05) were found in the groups treated with sodium pentaborate and paracetamol (APAP+B50 and APAP+B100) compared to the paracetamol groups (Fig. 2).

### Analysis of Apoptosis

Comparing the group in which sodium pentaborate was treated alone (B100) to the control group revealed no statistically significant change (*p*>0.05) in kidney tissue. Compared to the control group, the application of APAP resulted in a substantial increase in caspase-3 activity (*p*<0.05). The effect of APAP, which enhances the activity of caspase-3, decreased

sodium pentaborate pretreatment (B50-B100, Fig. 1). Also, the B100 group was more effective than the B50 group.

Activation of liver caspase-3, one of the most crucial apoptotic indicators, was increased in the APAP group than in the control group (*p*<0.05). In addition, there was no significant difference between the control group and the B100 group (*p*>0.05), although the caspase-3 activity reduced (*p*<0.05) in both sodium pentaborate groups administered with paracetamol (Fig. 2).

## Discussion

In this investigation on rats, it was determined if sodium pentaborate supplementation would moderate the adverse consequences (oxidative stress, inflammation, and apoptosis) of APAP toxicity. APAP is an inexpensive and dependable pain medication that is frequently used by people. Yet, widespread paracetamol use causes drug exposure in vivo. According to investigations, excessive paracetamol usage increases in the generation of reactive oxygen species (ROS), a reduction in the activity of antioxidant enzymes, and liver and kidney damage [3, 41]. After oral ingestion, the cytochrome p450 microsomal enzyme system in the liver metabolizes paracetamol to NAPQI, which is then detoxified by endogenous glutathione. When NAPQI is administered
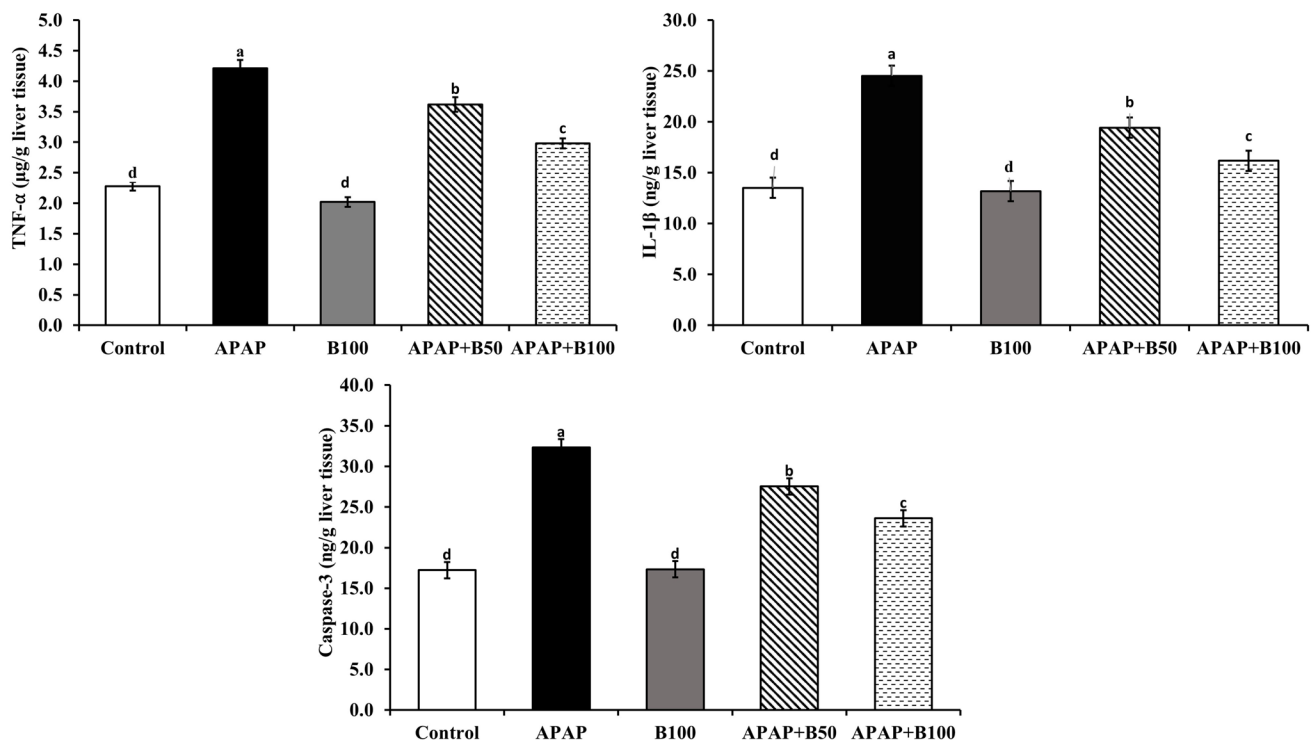
**Fig. 2** Effect of sodium pentaborate and APAP on TNF-α, IL-1β, and caspase-3 in rat liver tissue. Data represent the means ± SD of seven rats in each group. Results were derived from one-way ANOVA fol-lowed by Tukey's post hoc test. **a–d** Significant ($p < 0.05$) differences among groups

excessively, glutathione levels are inadequate, and no detoxi-fication occurs. It is believed that it exerts its harmful effects by covalently attaching to macromolecules such as proteins, lipids, and DNA; as a result, reactive oxygen species are produced in the cell [38, 42, 43]. When NAPQI is overpro-duced, glutathione levels are insufficient, and detoxification does not occur. It exerts its harmful effects by covalently binding to macromolecules such as protein, lipid, and DNA; as a result, reactive oxygen species are produced in the cell. A high quantity of NAPQI causes hepatic necrosis and, in its most severe form, liver failure [44] and kidney damage [41, 45]. According to studies, prolonged APAP consumption increases the risk of nephropathy and is directly associated with APAP [5, 46].

Urea, creatinine, BUN, and uric acid levels are the pri-mary indicators to assess kidney function. Increased plasma concentrations during reabsorption occur after toxic sub-stance exposure and may cause kidney damage [47, 48]. Different dosages of APAP induce renal tubular necrosis in humans and laboratory animals and raise blood urea and creatinine concentrations [3, 49]. In this study, the BUN and creatinine levels of the APAP group increased relative to the control group. However, both dosages of the sodium pentaborate supplement lowered the elevated levels. In research that used boric acid (50, 100, 200 mg/kg) to treat cisplatin nephrotoxicity, it was shown that the 50 and 100

mg/kg dosages did not affect BUN levels, whereas the 200 mg/kg dose significantly elevated BUN levels. In the same study that tested the effect of borax (5, 10, 20 mg/kg) on BUN levels, the 10 mg/kg dosage was shown to lower BUN levels. In the comparison of serum creatinine levels with the cisplatin group, it was underlined that 200 mg/kg boric acid and 5 mg/kg borax raised creatine levels, although other boric acid and borax dosages did not impact serum creatine levels [50]. In research where boric acid (5, 10, 20 mg/kg) was administered orally to rats to treat acrylamide toxicity, plasma BUN levels fell dose-dependently, but creatine lev-els remained unchanged [51]. In contrast to the previously mentioned study, it was shown that both dosages of sodium pentaborate lowered BUN and creatinine levels, which were raised by paracetamol.

Paracetamol is extensively used as an analgesic and anti-pyretic by the populace. In the case of hepatotoxicity due to medication, liver enzymes are tested [8, 52]. Alkaline phosphatases and transaminases are present in the cell, and their release into plasma or serum is one of the most cru-cial indicators of liver damage [53, 54]. The degree of liver damage is determined by the extent of the rise in the activity of these enzymes [55, 56]. According to many researchers, APAP-induced toxicity increases serum transaminase activ-ity. In this investigation, we found that ALT, AST, and ALP enzyme activities rose in the APAP group, while sodium

pentaborate supplementation reduced these enzyme activities in the blood.

Various processes in metabolism generate ROS (peroxides, superoxide anion radicals, etc.), which induce oxidative stress. Thus, major cellular impairments such as lipid peroxidation, protein denaturation, and DNA damage occur in the membrane [57, 58]. The amount of MDA, an indication of lipid peroxidation, increases due to rising oxidative damage. Antioxidants (SOD, CAT, GSH, and GPx), which play crucial roles in the body's defensive mechanism, are diminished by oxidative stress. GSH is one of the most commonly employed nonenzymatic antioxidants against a swath of reactive agents resulting from the toxicity of various substances and for the protection of other enzymatic antioxidants. The most prominent adverse impact of APAP toxicity is the consumption of GSH stores by a NAPQI metabolite [59, 60]. Depletion of GSH induces oxidative stress, necrosis, and apoptosis in tissues, particularly the liver and kidney [5, 44, 61]. Ucar et al. observed that during APAP-induced nephrotoxicity (1g/kg), the APAP group's kidney MDA level increased dramatically while GPx activity decreased [35]. Multiple studies have demonstrated that APAP administered to rats at varying dosages decreases SOD, CAT, GPx, and GSH levels in the kidney [45, 62]. APAP decreases liver SOD, CAT, and GPx enzyme activities and increases MDA levels [62, 63]. Boron has a favorable effect on antioxidant capacity and reduces DNA damage and lipid peroxidation, according to many studies in which boric acid and borax are employed together or individually [30, 50, 64]. It was observed that boric acid supplementation at various dosages (5, 10, and 20 mg/kg) in the kidneys of rats with malathion-induced oxidative stress protected against toxicity and increased antioxidant enzyme activity [65]. In a separate investigation, it was shown that a 28-day boric acid supplement (100 mg/kg) administered to rats with arsenic-induced nephrotoxicity lowered the MDA level in kidney tissue and boosted antioxidant capacity (GSH, SOD, CAT) [66]. In addition, Turkez et al. reported that boron compounds administered at a concentration of 15 mg/L increased the SOD and CAT activities of erythrocytes, but the addition of 500 mg/L boron reduced these activities [32]. Ince et al. noted that treatment with 100 mg/kg boric acid or borax for 28 days did not significantly modify the plasma antioxidant capacity compared to that of control animals [30]. In this study, it was shown that in addition to reducing lipid peroxidation, boron can also improve the body's antioxidant defense system and prevent tissue damage. However, Mohora et al. demonstrated a decrease in GSH levels in the liver tissue of rats given 40 mg/kg boric acid for 90 days [67]. Boron application to rats lowered liver MDA levels and enhanced SOD, CAT, GPx, and GSH levels, similar to the research findings listed in the review of the relevant literature. It has been determined that lipid peroxidation can be avoided, and antioxidant defense can be strengthened by administering B50 and B100 dosages.

Cytokines are polypeptides produced and secreted by cell types. They play a vital function in regulating inflammatory and immunological responses in the organism's neurological systems. TNF-α, among the first released cytokines in high-level infections, is the primary marker of an acute inflammatory response. It is produced in large quantities and is associated with systemic and pathological events [68]. IL-1β, a key mediator of the inflammatory response, is involved in advantageous cellular functions such as proliferation, differentiation, and death [69]. IL-33, which can have both pro-inflammatory and anti-inflammatory effects, is a nuclear cytokine expressed from IL-1β and shows similar properties [17]. In several investigations where boron supplementation was administered, it was shown that boron supplementation decreased TNF-α levels, enhances the immune system, and increases the inflammatory response [14]. In this study, inflammation markers TNF-α, IL-1β, and IL-33 levels increased with high-dose APAP and both doses of sodium pentaborate decreased these levels in a manner consistent with the existing literature. Caspase-3 is one of the effector caspases in apoptosis and is responsible for the breakdown of the cellular skeleton [70, 71]. In a research conducted by Eldutar et al., the administration of 500 mg/kg of paracetamol to rats dramatically boosted liver caspase-3 activity [72]. In this investigation, it was discovered that while the liver caspase-3 activity was enhanced in the paracetamol group, both dosages of sodium pentaborate administration lowered the liver caspase-3 activity, confirming that the acquired findings were consistent with the published literature.

## Conclusions

In conclusion, the findings of this research demonstrate that administering acetaminophen at a dose of 1 g per kilogram of body weight orally can result in liver and kidney damage, as evidenced by increased levels and activity of liver function tests and kidney function tests. However, pretreatment with boron for 6 days can significantly reduce the levels and activities of other hepatic and renal biomarkers, including MDA, TNF-α, IL-1β, IL-33, and caspase-3, while increasing the levels of SOD, CAT, GSH, and GPx. These results suggest that sodium pentaborate, a rare molecule utilized as a boron source, possesses antioxidant, anti-inflammatory, and anti-apoptotic properties that may be advantageous in managing APAP-induced tissue damage. Based on the presented data, the protective effects of sodium pentaborate against APAP toxicity are mainly mediated by its ability to reduce oxidative stress. In order to ascertain the precise mechanism of effect of sodium pentaborate, a thorough assessment of its clinical effects using histopathological and

immunohistochemical studies is important. Within the scope of this study, sodium pentaborate was subjected to evaluation concerning its antioxidant, anti-inflammatory, and anti-apoptotic activities, with the potential for future studies to corroborate these findings through other clinical observations. In summary, this study propose that sodium pentaborate may be a promising treatment option for APAP-induced toxicity.

## Declarations

**Conflict of Interest** The authors declare no competing interests.

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