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RESEARCH

Boric Acid (Boron) Attenuates AOM-Induced Colorectal Cancer in Rats by Augmentation of Apoptotic and Antioxidant Mechanisms

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Abstract

Boric acid (BA) is a naturally occurring weak Lewis acid containing boron, oxygen, and hydrogen elements that can be found in water, soil, and plants. Because of its numerous biological potentials including anti-proliferation actions, the present investigates the chemopreventive possessions of BA on azoxymethane (AOM)-induced colonic aberrant crypt foci (ACF) in rats. Thirty laboratory rats were divided into 5 groups: negative control (A) received two subcutaneous inoculations of normal saline and nourished on 10% Tween 20; groups B–E had two injections of 15 mg/kg azoxymethane followed by ingestion of 10% Tween 20 (B, cancer control), inoculation with intraperitoneal 35 mg/kg 5-fluorouracil injection (C, reference group), or ingested with boric acid 30 mg/kg (D) and 60 mg/kg (E). The gross morphology results showed significantly increased total colonic ACF in cancer controls, while BA treatment caused a significant reduction of ACF values. Histopathological evaluation of colons from cancer controls showed bizarrely elongated nuclei, stratified cells, and higher depletion of the submucosal glands than that of BA-treated groups. Boric acid treatment up-surged the pro-apoptotic (Bax) expression and reduced anti-apoptotic (Bcl-2) protein expressions. Moreover, BA ingestion caused upregulation of antioxidant enzymes (GPx, SOD, CAT), and lowered MDA contents in colon tissue homogenates. Boric acid–treated rats had significantly lower pro-inflammatory cytokines (TNF-α and IL-6) and higher anti-inflammatory cytokines (IL-10) based on serum analysis. The colorectal cancer attenuation by BA is shown by the reduced ACF numbers, anticipated by its regulatory potentials on the apoptotic proteins, antioxidants, and inflammatory cytokines originating from AOM-induced oxidative damage.

Keywords Colon cancer · ACF · Boric acid · cytokines · Histology · Immunohistochemistry

Abbreviations

ALT	alanine tranferase
AOM	azoxymethane
Bax	Bcl-2-associated X protein
Bcl-2	B cell lymphoma-2
CAT	catalayse
FU	fluorouracil
GPx	*glutathione* peroxidase
H and E	hematoxylin and eosin
IBD	irritable bowel disease
IL-10	interleukine-10
JAK/STAT	Janus kinase/signal transducers and activators of transcription
LDH	lactate dehydrogenase
LNCaP	lymph node androgen-dependent human prostatic carcinoma cell
MDA	malondialdehyde
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
OECD	*Organization for Economic Co-operation and Development*
SOD	superoxide dismutase
TNF-α	tumor necrosis factor α

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Introduction

Colorectal cancer (CRC) is a deleterious malignant neoplasm recognized as the third dominant leading risk factor of death-associated cancer worldwide. And it is the second leading cause of mortality-related cancer when statistics were combined from both genders [1, 2]. The risk factor

for acquiring colorectal cancer is slightly higher in females (1–26) than in males (1–23) during their lifetime. However, this range changes based on colorectal risk factors such as stress, alcohol, malnutrition, smoking, and obesity [3]. Despite pharmaceutical revolutionary innovations for designing effective anti-cancer drugs against colorectal cancer, all of these synthetic chemicals come with many drawbacks in the short and long terms, including hair loss, neuropathy, nephropathy, digestive problems, and sexual disability [4]. Therefore, searching for alternative natural medicines (chemoprotectives) with lower side effects is crucial for lowering the mortality and morbidity rates related to colorectal cancer. Alternatively, natural products from various environmental resources have been shown to be excellent cancer inhibitors without any of the mentioned side effects. For example, boron (mainly boric acid and borax) has shown different biological activities such as antimicrobial [5], antioxidant [6], anti-inflammatory [7], and anticancer actions [8].

Boron is a trace element commonly found as boric acid in water, soil, and herbs. Boron has been utilized as an active ingredient in the preparation of disinfectants, cosmetics, and pharmaceuticals. Although boron is chiefly detected in plants, many studies have shown a reduced amount of this element in animals, including humans, which may play an important physiological role that is yet to be understood. Scientists hypothesized two theories to explain the physiological role of boron in animals. First, the boron compound could be involved in the membrane receptors that respond to outside signals, including transmembrane signaling and binding to particular hormones, or controlling ionic movements [9]. Second, boron may play a role in the metabolic process through participation in the activation of enzymatic cascades [10]. Moreover, numerous studies have shown the metabolic roles of boron in the synthesis and break down of minerals (calcium and phosphate) [11], enzymes [12], 1,25 (OH) dihydro cholecalciferol [13], and hormones [14], as well as facilitation of protein and lipid metabolism [12]. Scientists declared that the healthy tolerable amount of boric acid would be 150 mg/kg (1–3 mg/kg daily intake) and a deficiency (0.03 mg/kg) or above normal value could be detrimental to human health [15].

Throughout history, boric acid has been utilized industrially for making many products (laundry detergents, pesticides, fertilizers, eye and mouthwashes, skin powders, flame retardants, ointments, and cleaning agents) [16, 17] and pharmacologically for treating many human diseases, including fungal infection (vaginal candidiasis [18] and *Candida albicans* [19]), urinary tract infection [20], wound healing in diabetic rats [21], microbial infection and bone defects [22], inflammation, and oxidative stress in rats exposed to renal injury [23]. BA has also been used in poultry litter to regulate darkling beetles [24]. Recently, scientists have reported BA as an effective agent for thermal energy storage [25]. In vitro, anticancer studies have shown significant biological action of BA against the growth of different cancer cells, prostate cancer [26], cervical cancer [27], and colon cancer cells [28]. BA can have attenuated effects on ovarian damage caused by ischemia-reperfusion, which could be due to its antioxidant, anti-inflammatory, and anti-apoptotic actions [29].

Oxidative stress is a highly complicated process resulting from an imbalance between the formation and elimination of ROS and reduced antioxidant enzymes [30]. Lipid peroxidation is a biological phenomenon involving the breakdown of lipids and the release of reactive substrates that may disturb membrane rigidity, fluidity, and allowance to macromolecules. For example, 4-hydroxynonenal (HNE) is a by-product of lipid production with increased electrophilic characteristics that can rapidly interact with either reduced molecular weight chemicals (glutathione with proteins) or macromolecules such as DNA, forming a covalent bond and disrupting various biological processes. Oxidative stress and lipid peroxidation byproducts have been found to be two major risk factors associated with many human disorders, including inflammation, atherosclerosis, neuropathy, nephropathy, and cancer [31]. Natural products can reduce the negative impact of ROS and lower oxidative stress–related damages. For example, boron has been found to be an inhibitor of oxidative damage possible through its enhancement impact on the glutathione formation or facilitation process of neutralization of ROS molecules [32].

Inflammation is a series of pathological processes that can be initiated as a result of prolonged oxidative stress, including stimulation of the NF-κB mechanism, increased expression of cyclooxygenase-2 (COX-2), and production of NO by inducible nitric oxide synthase (iNOS) [33]. Moreover, inflammation may also result from the pathogenic entrance that leads to upregulation of the pro-inflammatory cytokine, tumor necrosis factor-alpha (TNF-α), interleukin-6, IL-8, chemokines CCL2, and CXCL8, while reducing anti-inflammatory cytokines (IL-10). Chronic inflammation (CI), a long-term health defect, has been correlated with a lifelong series of diseases, namely atherosclerosis, cardiovascular diseases (CVD), inflammatory bowel disease (IBD), kidney disease, and diabetes mellitus. CI is labeled as one of the main leading causes of death worldwide, according to a recent estimation, which stated that 50% of all deaths are due to inflammation-related diseases and autoimmune diseases [34]. IBD is an inflammatory-related gastrointestinal disease recognized by disruption of the intestinal epithelium (intestinal barrier), which usually prevents penetration of pathogens and toxic compounds and permits the passage of only certain macromolecules (nutrients and electrolytes) through different ion and protein channels. Chronic inflammation can disrupt the characteristic selective permeability of the intestinal defense layer, causing the passage of macromolecules (pathogens,

exotoxins, and fats) from the lumen into the intestinal tissue, commonly known as leaky gut; consequently, this will lead to colorectal cancer. Therefore, controlling inflammation is a crucial step toward the prevention of colorectal cancer, especially in IBD patients [35]. Despite numerous investigations (in vitro and in vivo) on the pharmacological potentials of BA, however, its in vivo colon cancer cytotoxicity and its underlying mechanism are yet to be found.

Herein, we rationally designed the current experiment to evaluate the chemoprotective potentials of BA in AOM-induced oxidative stress-mediated colorectal cancer in rats. Here we studied the in vivo gross morphology, colonic histopathology, immunohistochemistry, antioxidant enzymatic and non-enzymatic, inflammatory cytokines, and blood biochemical parameters of AOM-induced colorectal cancer in rats supplemented with two different doses of BA for 2 months.

Materials and Methods

Chemicals

Boric acid powder was bought from Sigma-Aldrich Chemical Co. (Merk, Germany). The powder was mixed with 10% Tween 20 and delivered to rats in an amount of 5 mL/kg in two different doses, 30 and 60 mg/kg [36].

Ethic Approval for the Animal Experiment

The current experimental rats were in parallel with the Iraqi guidelines for animal handling and the National scientific recommendations for laboratory animals [37]. The experimental protocol was confirmed by the Ethics Committee of Cihan University-Erbil (BIO/11/12/2022/M.A.A.).

Acute Toxicity

To verify the safe dosage of boric acid, an acute toxicity test was applied to rats. Thirty-six Dawley male (18) and female (19) rats (180–200 g) aged 7–8 weeks were obtained from Cihan University-Erbil. The animals were fed on standard diet pellets and tap water and moved into dissociated cages with a wide-mesh wire bottom to escape coprophagia. For adaptation purposes, rats remained in their cages (without any treatment) for 7 days. Rats (30) were randomly segregated into 3 cages: group 1 (normal control) received 10% Tween 20; group 2, administered 30 mg/kg of BA; group 3, rats dieted with 300 mg/kg of BA based on the OECD guideline [38]. Before 24 h of delivering the treatment, rats had no access for food (only water). The supplementation of BA was performed by oral gavage to deliver single dose of 30 and 300 mg/kg for rats in the G2 and G3 groups, respectively. Food was removed for a further 3 to 4 h after BA ingestion, and the observation began immediately after treatment and continued for 48 h (every 30 min) for any possible toxic effects or changes in behaviors and physiology. Mortality, if any, was also reported after the experimental period. Directly after 2 weeks, rats were given xylazine and ketamine before the sacrifice. Blood was collected from an intracardial puncture, and then, serum specimen was transferred to a centrifuge (LC carousel, Roche, Germany) for biochemical analysis [39]. The liver and kidney were also collected from rats for investigation of any histological changes that may occur to due BA dosage [40].

Chemoprotection procedure of BA

Thirty adult male Dawley rats (180–200 and aged 7–8 weeks) were divided equally into 5 cages (6 rats in each): A, normal control rats; B, cancer control rats; C, reference rats; D, rats received 5-fluorouracil (5-FU); and D and E, rats were supplemented with a low and high dose of BA [39].

Normal control rats received a saline solution 0.09% subcutaneously and rats in group B-E were given two doses of 15 mg/kg AOM in 2 weeks by subcutaneous injection. In addition, normal and cancer control rats were given 10% Tween 20 (5 mL/kg); reference rats received 35 mg/kg of 5-FU once a week for 4 weeks by intraperitoneal injection, and BA-treated rats received 30 and 60 mg/kg by oral gavage for 2 months (Fig. 1). After that, rats were given anesthesia and were sacrificed, and the collected colon tissues were examined for the degree of ACF formation by different histopathology techniques. Colon tissue specimens underwent the homogenization process [41].

Evaluation of ACF Scores

The experimental rats were given anesthesia, and were sacrificed, and the colon tissues were mixed with cold phosphate-buffered saline (PBS). The colon tissues were cut longitudinally from the bottom to the rectum. After that, tissues were colored with methylene blue dye (0.2%) for the microscopic examination and evaluation of the ACF degree. The ACF scores were determined for each tissue specimen by estimation of ACF in different microscopic focus [39].

Inhibition (%) = Total no. of foci in negative control/ no. of foci in each group × 100

Histology Procedure of ACFs

Colon tissue samples were mixed with buffered formalin (10%) before processing them for the tissue machinery (Leica, Germany). After that, tissues were blocked with paraffin, and a regular slice of 5 µm was fixed on slides and colored with hematoxylin and eosin (H&E). The histological examination of stained tissues was displayed by using a light microscope (Nikon, Japan) [42].

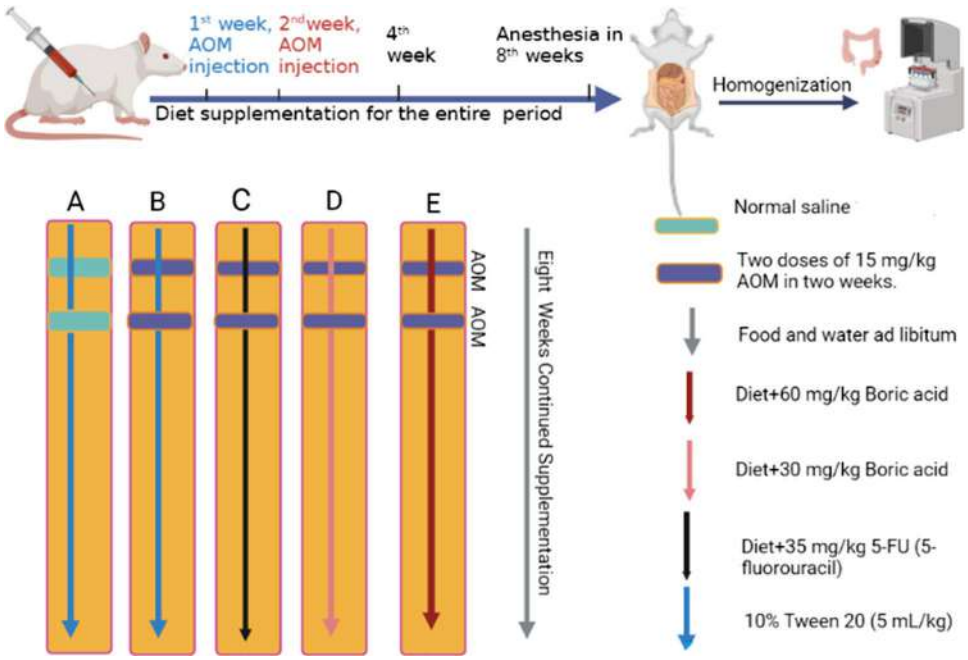

Fig. 1 Schematic timeline of experimental design. Created in Biorender. **A** Normal control rats; **B** cancer control rats; **C** reference rats; rats received 35 mg/kg 5-FU (5-fluorouracil); **D**, **E** rats were supplemented with 30 and 60 mg/kg BA

Immunohistochemistry

The immunohistochemistry of natural products and potential herbal medicinal was commonly measured by the estimation of the expression of Bax and Bcl-2 proteins [43]. Briefly, colon tissues have undergone a process of de-paraffinization and rehydration and have been mixed with 10 mM sodium citrate buffer (10 min) for antigen retrieval. The temperature of tissue samples was cooled down by Tris-buffered saline before the antioxidant procedure using an ARK peroxidase kit (DAKO Denmark A/S, Glostrup, Denmark). The colon tissues were transferred into the peroxidase solution to allow the blockage of endogenous hydrogen peroxidase 0.5% (5 min). Finally, colon tissues were undergone dehydration and the incubation procedure (20 min) by biotinylated antibodies versus Bax and Bcl-2 (Elabscience, USA) followed by the addition of streptavidin–HRP (nutrient) and deepening in 3-3-diaminobenzidine as chromogen for 10 min. After washing, the slides were transferred to hematoxylin stain, dried, and mounted for microscopic examination.

Antiradical Evaluation of Homogenized Colon

The dissected colons were washed in an ice-cold saline solution, and then a small portion of colon tissue (10% w/v) was mixed with ice-cold phosphate buffer for the preparation of the homogenization process by the homogenizer at (50 mM, pH 7.4). The produced mammalian protease inhibitor cocktail was centrifuged (30 min at 10,0006*g* at 4uC) and the supernatant was moved into separate tubes for the estimation of the antioxidant enzymes (CAT, SOD, GPX) and MDA contents (kits from Elabscience, USA) [44].

Biochemical Analysis

Blood samples were obtained from the intracardial puncture of experimental rats and centrifuged for laboratory investigations. The liver and kidney parameters were detected in AOM-induced ACF in rats by using specialized Cobas commercial rat kits in an automatic analyzer, Cobas c311 (Roche, USA) [45].

Statistics

The current statistical data are presented as the mean ± SEM obtained from triplicate estimations. The statistical method for the current study was one-way analysis (ANOVA, SPSS software) and GraphPad Prism 9.0. The current significant value was set at $P< 0.05$.

Results

Acute Toxicity

The current results present the non-toxic effects of BA supplementation in two different doses, 30 and 300 mg/kg, for 14 days. Continuous observation (every 8 h) did not reveal any abnormal characteristics in the physiology or appearance of rats. Moreover, physical activity and feed intake were very comparable between BA-ingested rats and normal

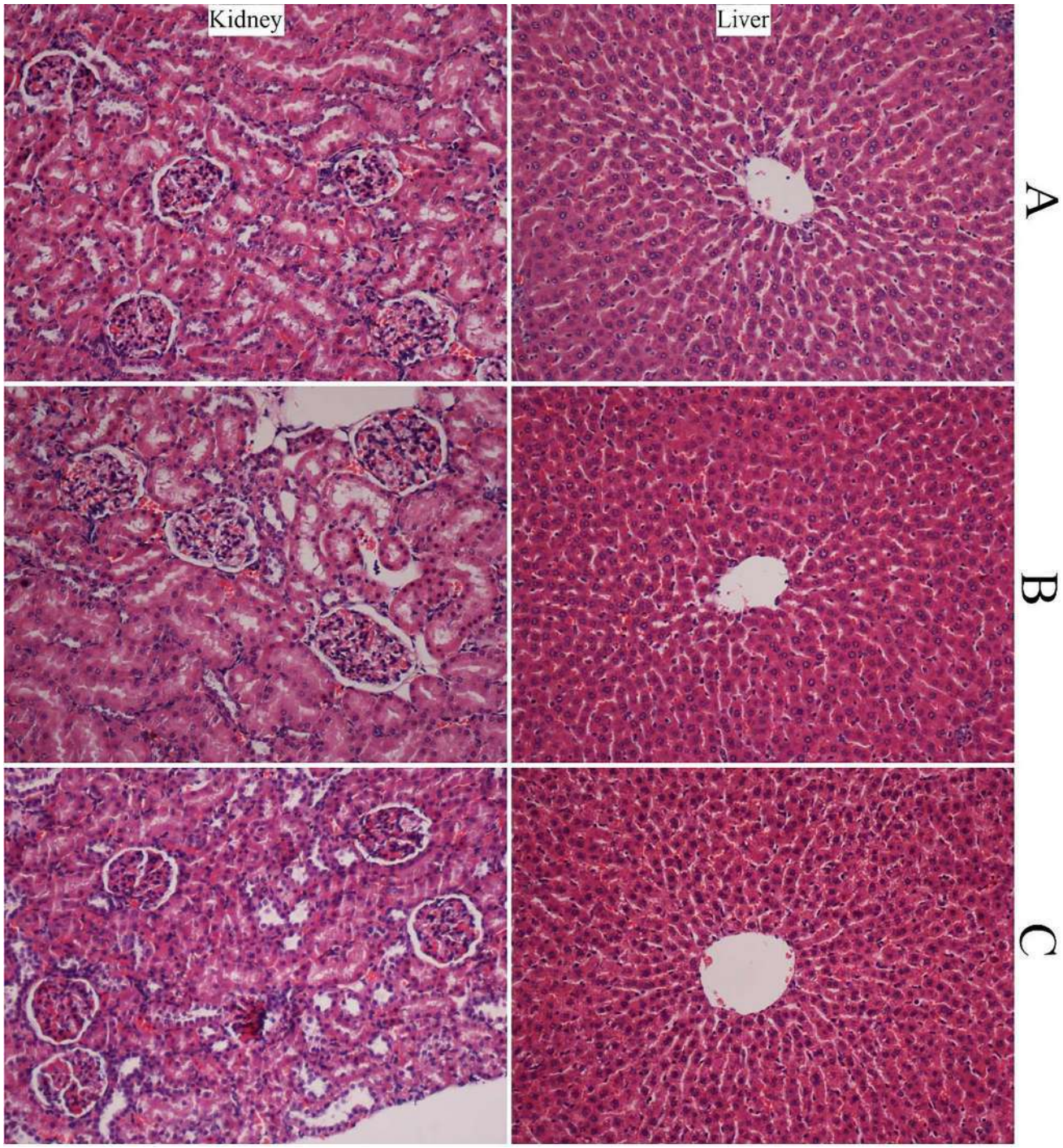

Fig. 2 Histology of liver and kidney in acute toxicity test. **A** Normal control rats; **B** rats received 30 mg/kg of BA; **C** rats received 300 mg/kg of BA (magnification, 20×)

results have shown significant variables in the concentrations of inflammatory cytokines in colon tissue homogenates between experimental rats (Fig. 8(A–E)). Normal control rats (Fig. 8(A)) had notably the lowest values of TNF-α and IL-6 and the highest level of IL-10 compared to all experimental rats. Cancer control rats (Fig. 8(B)) dieted with only AOM had statistically the highest value of pro-inflammatory cytokine contents (TNF-α and IL-6) and the lowest anti-inflammatory cytokine levels (IL-10) in their tissue homogenates. Boric acid treatment leads to positive augmentation of inflammatory status in the colon homogenates, which very similar to that of 5-FU treated rats as shown in Fig. 8(C,

c, while the Bcl-2 protein has been commonly referred to as an anti-apoptotic factor that preserves the outer membrane integrity of the mitochondria (a key player as an apoptotic inhibitor of both intrinsic and extrinsic pathways.). The present study has shown a reduced appearance of Bax and increased expression of Bcl-2 in AOM-treated rats. Consequently, the imbalance between these two protein expressions leads to cellular dysfunctionality and changes in the mitochondrial route of apoptosis [63]. In this context, rats supplemented with boric acid presented significantly higher Bax protein and lower Bcl-2 protein concentrations in their colon tissues, which activated pro-apoptotic factors such ascaspase-9 and caspase-3. Furthermore, histological views of colon tissues showed lower proliferation levels with reduced values of cells that are out of their normal cycle (labeling index). Similarly, numerous researchers have shown the BA potential in the positive modulation of apoptotic proteins through different immunohistochemical techniques [64]. Studies have repeatedly validated the anti-apoptotic roles of boron (boric acid) through its impact on the expression of Bax/Bcl-2 proteins [65, 66]. In this context, researchers have reported fewer Tumors, viable cells, and fewer androgen receptor-positive cells in the boron-supplemented rats with larger necrotic areas compared to cancer controls, which had increased androgen receptor expression and numerous viable LNCaP cells. Moreover, localization of IGF-1 by immunostaining assay revealed a noticeably reduced expression of IGF-1 in BA-treated rats [51]. Scientists explained the anticancer mechanisms of boron through its involvement in different enzymatic actions, including NAD-dehydrogenases, serine proteases, mRNA splicing, cell division, receptor blocking, and the initiation of apoptosis. Data analysis has shown that boron-enriched foods were significantly associated with decreased incidence of cervical and prostate cancers, and reduced rate of lung cancer in female smokers, thus suggesting new chemoprotective strategies including boron supplementation as promising alternatives for better management of cancer cell proliferation [67].

Reactive oxygen species, along with other internal and external factors, can stimulate inflammatory cytokine releases and increase inflammatory responses, which activate the cascade of initiation, development, and prognosis of inflammatory bowel disease (IBD) [68]. IBD is a digestive tract disease that mainly affects the large intestine, which could be hereditary or result from non-genetic risk factors such as oxidative stress (key pathophysiological). IBD primarily includes Crohn's disease and ulcerative colitis, which are similar in terms of origin (immunologic overreaction) and differ in their involvement in the digestive system [69]. Moreover, oxidative stress studies have shown the transformation of sensory cells into neoplastic cells in many IBD cases [70]. Therefore, carcinogenesis in the digestive system (colon) includes a sophisticated process that initiates gradually and instantly along with oxidative stress involvement [71, 72]. The present work revealed significant antioxidant potentials of BA (30 and 60 mg/kg) represented by upregulation of SOD and CAT, and GPx, and downregulation of lipid peroxidation (MDA) levels in colon tissue homogenates. Similarly, researchers have shown the antioxidant potential of BA (30–100 mg/kg) in different in vitro and in vivo animal trials [7, 47]. Researchers have found that boron supplementation (up to 160 mg) was associated with upregulation antioxidant enzymes and significantly reduced cellular apoptosis, while increased dosages such as 650 mg/kg reversed the positive augmentation of boron and stimulated apoptotic factors [64]. Moreover, boron ingestion showed significant antioxidant potentials represented by upregulating SOD, glutathione peroxidase, glutathione-S-transferase, and CAT levels in erythrocytes, while increasing the dose (500 mg/kg) downshifted the antioxidant enzymes and caused severe oxidative-related tissue damage [73]. Similarly, borax ingestion in rats for three consecutive days, followed by thioacetamide administration (400 mg/kg), lowered thioacetamide-hepatic tissue damage, possibly through augmentation of antioxidants and oxidative stress in affected tissues [74].

NF-κB is a key modulator in the initiation and development of immune responses and different inflammatory processes. It also facilitates the activation of pro-inflammatory cytokines, IL-6, TNF-α, and prostaglandins. Previous studies have validated that AOM can effectively stimulate the production of inflammatory cytokines and other inflammatory mediators [39, 75]. Moreover, TNF-α, along with IL-1β, can activate the formation of the metalloproteinase enzyme and modulate COX-2 overproduction during the early phases of carcinogenesis. Interleukin 6 (pro-inflammatory) can activate the JAK/STAT signaling pathways, preventing apoptosis, and, along with TNF-α, facilitating angiogenesis and cancer growth [76]. In the current study, rats receiving only AOM had significantly increased IL-6 and TNF-α cytokines and notably reduced anti-inflammatory cytokines (IL-10) in their blood. Conversely, BA lowered immune and inflammatory responses, as indicated by the up-modulation of IL-6 and TNF-α and the down-augmentation of IL-10 cytokines in rats. Accordingly, scientists have shown boron efficacy in down-regulating pro-inflammatory cytokines (IL-6) in experimental diabetic rats [77].

The current study revealed that boron supplementation maintained biochemical parameters within the normal range in AOM-induced aberrant foci in rats. Accordingly, boron supplementation in drinking water in male mice for 60 days caused positive modulation of liver enzymes (LDH and ALT), while serum albumins were not affected by the boron ingestion [78]. Kremer et al. have shown that dietary intake rich in boron (fruit, win, and nuts)

is associated with the positive augmentation of kidney function parameters and the long-term survival of kidney transplant recipient patients [79]. The literature cited above validates BA as a bioactive ingredient against various human diseases, including chemoprotection against colorectal cancer.

Conclusion

To our best knowledge, the present research is considered the first data on the chemoprotective effects of BA on AOM-induced foci in rats. The acute toxicity evaluation of 2-week BA ingestion revealed the absence of any behavioral or physiological changes in rats. Our data present notable cytoprotective potentials of BA against AOM-induced colon cancer in rats. The underlying mechanism of chemoprotective potentials could be correlated with their positive modulation of pro- and anti-apoptotic proteins, antioxidant enzymes, and inflammatory cytokines, and maintained liver and kidney functionalities. Accordingly, the outcomes suggest boric acid as a bioactive agent that might provide a new template for the design of potential pharmaceuticals targeting colorectal cancers.

Author Contribution A. A.j., M.A.A., structure and design; Z.Z.A., A.A.J, M.A.A., methodology; N.A.S., S.M.A., N.A.S.,R.R.H., data analysis; I.A.I., R.A.A., H.A.A., M.M.G., I.A.I., R.A.A.,Y.A.A., resources and validation; W.F.F., Y.A.A., M.M.A., G.A.B., software; A.A.J., G.A., writing original draft.; all authors read and approved the final manuscript.

Data Availability Further information are available on request.

Declarations

Statement of Ethics The current animal study was approved by the ethics committee in Cihan University-Erbil (Ethical No. BIO/15/10/2022/MAA).

Conflict of Interest The authors declare no competing interests.

Informed Consent Not applicable

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