



Chemoprotective effect of boeravinone B against 1,2-dimethyl hydrazine induced colorectal cancer in rats via suppression of oxidative stress and inflammatory reaction

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Background: Colorectal cancer (CRC) has few or no symptoms and is often diagnosed at its end stage. Boeravinone B (BB) is a natural rotenoid which induces an antioxidative effect and has been used in cancer prevention. In this study, we scrutinized the chemoprotective effect of BB against 1,2-dimethyl hydrazine (DMH) induced CRC in rats.

Methods: Subcutaneous administration of DMH (40 mg/kg) was used for the induction of CRC in rats, followed by oral administration of BB. The body weight, tumor volume, tumor incidence, and total number of tumors were estimated in all rat groups rats except the normal group. Antioxidant parameters, phase I and II enzymes, and inflammatory cytokines and parameters were estimated at the completion of the study.

Results: DMH induced group rats exhibited a tumor incidence of 100% along with several tumors/polyps per tumor-bearing rat, while BB treatment remarkably suppressed the incidence of tumors and suppressed polyps per tumor bearing rat. BB treatment significantly ($P < 0.001$) altered the level of antioxidant parameters, phase I and phase II enzymes, and cytokines such as TNF- α , IL-1 β , IL-4, IL-6, and IL-10, and treatment significantly ($P < 0.001$) suppressed the level of inflammatory cytokines, including cyclooxygenase-2 (COX-2), prostaglandin E₂ (PGE₂), and inducible nitric oxide synthase (iNOS).

Conclusions: BB treatment considerably suppresses colon cancer via its antioxidant and anti-inflammatory mechanism.

Keywords: Colorectal cancer (CRC); boeravinone B (BB); oxidative stress; inflammation

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Introduction

Cancer is a major cause of mortality and morbidity globally, and colorectal cancer (CRC) is the 3rd most common type in men and women (1). Reports suggest dietary habits and genetic susceptibility can increase the risk of the disease (2), and that a controlled diet may suppress this risk.

DMH is a potent carcinogen commonly used for the induction of colorectal tumors in the rodent model. DMH induces CRC in multiple steps involving discrete microscopic lesions (aberrant cryptic foci) (3,4). Previous reports suggest an active metabolite of DMH excreted via bile is mainly accountable for its carcinogenic effect on colorectal tissue while passing through the digestive system (4). DMH specifically targets DNA and finally induces a generation of methyl adducts with bases of DNA, micronuclei, and mutation, yielding macroscopically visible neoplasms (5). During the metabolism of DMH, methylazoxymethanol and azoxymethane are generated, which also move to colorectal tissue through blood or bile to produce their ultimate carcinogenic metabolite (diazonium ion). This further induces oxidative stress via methylating the biomolecules of colonic epithelial cells leading to promutagenic events as a result of tumor promotion and inflammation (1,6,7).

High reactive oxygen species (ROS) exhibit alteration in various signalling pathways related to the drug resistance, proliferation, invasion, metastasis and survival of tumors (1,8). However, the human body has a unique system for adjusting the level of ROS, as endogenous antioxidant enzymes such as glutathione peroxidase (GPx), superoxide dismutase (SOD), paraoxonase1 (PON1), and catalase (CAT) play crucial roles in suppression it (1,9). Other markers such as phase II detoxification enzymes offer protection from drug toxicity and carcinogenesis effects. Glutathione S transferase (GST), with the help of glutathione (GSH), catalyzes the conjugation electrophilic compound, and quinone reductase (QR) catalyzes the two-electron reduction of nitrogen and quinone oxides (7,10).

The inflammatory reaction plays a crucial role in the expansion of tumors, and previous reports suggest inflammation and oxidative stress facilitate the progression of CRC (10,11). Cancer also increases the level of inflammatory mediators including cyclooxygenase-2 (COX-2). Various pathological and physiological conditions also play a crucial role in the expansion of tumors and the inflammatory reaction. Inflammatory cytokines such as TNF- α participate in the initiation and progression of CRC (4), while the

increased level of inflammatory cytokines enhances the level of nuclear factor kappa B (NF- κ B).

GDI2 is a GDP dissociation inhibitor 2 which belongs to the small family of chaperone proteins and shows a significant signal transduction molecule which regulates the expansion of various types of cancers including that of the prostate, breast, and thyroid, as well as CRC (12). Various research suggests GDI2 is heavily involved in the regulation of several biological functions including apoptosis, tumor cell proliferation, and cell metabolism and migration (13-15). Therefore, while the function of GDI2 has been previously explored in various types of the cancer, its role has not been explored in the colorectal cancer.

Boeravinone B (BB) is a rotenoid phytoconstituent belonging to the flavonoid family isolated from the *Boerhaavia diffusa* (16), and previous reports have suggested it has an anticancer effect (17,18). BB also showed a protective effect against acute myoskeletal dysfunction, spondylosis, osteoarthritis, systemic lupus erythematosus, and rheumatoid arthritis (17-21), and an immunomodulator effect against various autoimmune diseases by exhibiting both free radical scavenging activity and anti-inflammatory effects (16,17). In this study, we scrutinized the anticancer effect of BB against DMH induced CRC in rats. We present the following article in accordance with the ARRIVE reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-733/rc>).

Methods

Experimental animals

Swiss Albino Wistar rats (aged: 10–12 weeks; 200 \pm 20 g; sex-male) were procured from the animal house of Jinan University and kept in standard laboratory conditions at a temperature of 20 \pm 5 °C; humidity 60 \pm 20% and a cycle of 12 h dark and 12 h light. Animal experiments were performed under a project license (No. GDY2102322) granted by ethics committee of The Affiliated Hospital of Guangdong Medical University, in compliance with The Affiliated Hospital of Guangdong Medical University guidelines for the care and use of animals. A protocol was prepared before the study without registration.

CRC induction

A previously reported method with minor modification was used to induce CRC in the rats.

A subcutaneous administration of DMH (40 mg/kg) was used. Briefly, the toxicant (DMH) was prepared via dissolving into the saline solution and maintained the pH (6.5) using the NaHCO₃.

Tested groups

BB was administered to animals in the form of a suspension which was prepared via dissolving it in 1% of carboxymethyl cellulose (CMC).

Experimental design

After successful induction of CRC, rats were divided into groups as described below:

- ❖ Group I: this normal control group received the vehicle throughout the experimental study;
- ❖ Group II: this DMH control group received the subcutaneous administration of DMH (40 mg/kg) for 16 weeks;
- ❖ Group III: this DMH control group received the subcutaneous administration of DMH (40 mg/kg) for 16 weeks and oral administration of BB (5 mg/kg);
- ❖ Group IV: this DMH control group received the subcutaneous administration of DMH (40 mg/kg) for 16 weeks and oral administration of BB (10 mg/kg);
- ❖ Group V: this DMH control group received the subcutaneous administration of DMH (40 mg/kg) for 16 weeks and oral administration of BB (15 mg/kg).

Body weight and food and water intake were estimated at regular time intervals. At the termination of the experimental protocol, rats were anesthetized using diethyl ether, and blood was collected via puncturing the cardiac tissue and centrifuged at 15,000 rpm for 5 min to separate the serum. The serum sample was then separated out and kept at -20 °C for further analysis.

Antioxidant parameters

Phase I enzymes, including cytochrome C, cytochrome P450, and cytochrome B5, and phase II enzymes such as glutathione S transferase (GST) and UDP-glucuronyltransferase were estimated using a previously reported method with minor modification (3).

Previously reported method was used for the estimation of MDA via using the formation of thiobarbituric acid reactive substances (TBARS) (3,4). Tissue homogenate (0.2), sodium dodecylsulphate (0.2 mL of 8.1%), acetic

acid (1.5 mL), TBA (1.5 mL) were mixed together and finally made up the volume upto 4 mL using the distilled water and heated on water bath for 60 min at 95 °C. After cooling the sample added the n-butanol/pyridine (5.0 mL) and shaken vigorously and centrifuged for 10 min at 600 ×g. The pink coloured chromogen generates after adding the 2-thiobarbituric acid and estimation the absorbance at 535 nm.

For the estimation of SOD level, the reaction mixture was prepared using the Tris HCl buffer (2.875 mL), PMS (100 µL) and pyrogallol (10 mM HCl) and finally make up volume 3 ml and estimation the absorbance at 420 nm.

For the estimation of GPx activity, briefly, prepared the reaction mixture which contain the 0.1 M phosphate buffer (2 mL), hydrogen peroxide (0.95 mL) and PMS (0.05 mL) and finally make up to the volume 3 mL and determine the absorbance at 240 nm (3,4).

For the estimation of GPx activity, prepare the reaction mixture, which contain the EDTA (0.1 mL), sodium azide (0.1 mL), phosphate buffer saline (1.44 mL) glutathione reductase (0.05 mL), reduced glutathione (0.05 mL), NADPH (0.01 mL), H₂O₂ (0.01 mL) and PMS (0.1 mL) and estimation the absorbance at 340 nm (3,4).

The previous reported method was used for the determination of GR activity (3,4). Briefly, prepared the reaction mixture contains the PBS (1.65 mL), EDTA (0.1 mL), glutathione (0.05 mL), NADPH (0.1 mL) and PMS (0.1 mL) and make up the volume upto 2 mL and determined the absorbance at 340 nm.

Apoptosis

The level of apoptosis markers was estimated using available kits and following the manufacture's protocol.

Inflammatory cytokines and mediators

Inflammatory cytokines including interleukin-1β, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), and inflammatory mediators including prostaglandin E₂ (PGE₂), inducible nitric oxide synthase (iNOS), and COX-2 were estimated using enzyme-linked immunosorbent assay (ELISA) kits (MyBioSource Inc., San Diego, California, USA) as per the manufacture's instructions.

Reverse transcription-quantitative PCR (RT-qPCR)

A Trizol kit was used for the isolation of total RNA

Table 1 The incidence of colorectal tumor, tumor incidence and tumors/polyps per tumor bearing rats

No.	Group	No. of rats	Tumor bearing rats	Tumor incidence	Total number of tumor/polyps	No. of tumors/polyps per tumor-bearing rat
1	Normal	10	0	0	0	0
2	DMH	10	10	100	25	2.5
3	DMH + BB (5 mg/kg)	10	8	80	18	2.25
4	DMH + BB (10 mg/kg)	10	5	50	10	2
5	DMH + BB (15 mg/kg)	10	2	20	2	1

DMH, 1,2-dimethylhydrazine; BB, boeravinone B.

from cells (Invitogen, Thermo Fisher Scientific Inc.). For conducting the RT, the following conditions were maintained: 52 min incubation at 42 °C, followed by 5 min incubation at 85 °C to stop the reaction. Following this, RT-qPCR was carried out using SYBR Premix for mRNA PCR kits, while GAPDH was used as the internal standard. Thermocycling conditions used for performing the qPCR were as follows: initial denaturation for 30 s (95 °C), 5 s for 40 cycles (95 °C), and 30 s for (60 °C). The relative mRNA expression was accessed using the $2^{-\Delta\Delta C_q}$ analysis method. The primer sequence was as follows: GDI2 reverse primer 5'-TTTCGTCTCGAGGCTGTTAGTCTTCCCCATA G-3' and reverse primer 5'-CAACGGATACATTGGGGG TAGG-3' forwarded primer 5'-TTTCGTAAGCTTATGG ACGAGGAATACGATGT-3'.

Statistical analysis

The statistical significance of the results was estimated using one-way variance of analysis (ANOVA), and the significant difference between groups was scrutinized via Dunnett's multiple test. $P < 0.05$ was considered as significant.

Results

Tumors

Table 1 shows the number of rats bearing tumors. No tumors were observed in the normal control group rats, while the DMH induced group rats exhibited a 100% tumor incidence with 2.5 tumors/polyps per tumor bearing rat. BB treatment considerably suppressed the tumor incidence along with the no. of tumors/polyps per tumor bearing rat. BB (15 mg/kg) treated rats exhibited the maximum suppression of tumor incidence.

Antioxidants

Antioxidant parameters protect organs from oxidative injury. During the expansion and progression of disease, the level of antioxidant parameters suppresses and increases the production of free radicals, which further induce oxidative stress. DMH group rats demonstrated a boosted level of LPO and suppressed level of CAT, GSH, and SOD, while in DMH rats treated with BB, a significantly decreased LPO level and improved level of CAT, SOD, and GSH was seen (Figure 1).

Phase I and II enzymes

To explore a possible mechanism of action, we estimated the activity of phase I and II enzymes and found DMH induced group rats exhibited boosted levels of cytochrome P450 and cytochrome B5, while reducing glutathione reductase levels. BB treated group rats also significantly ($P < 0.001$) suppressed the level of cytochrome P450 and cytochrome B5, and boosted glutathione reductase levels (Figure 2).

The level of phase II like UDP-glucuronyltransferase and glutathione-S-transferase was estimated in the different group of rats. DMH group rats exhibited suppressed levels of UDP-glucuronyltransferase and glutathione-S-transferase, while BB treatment significantly ($P < 0.001$) enhanced these (Figure 3).

Cytokines

Cytokines play an important role in the expansion of cancer, and in this study DMH induced group rats exhibited boosted levels of TNF- α , IL-1 β , and IL-6, and reduced levels of IL-4 and IL-10. BB treated rats had significantly

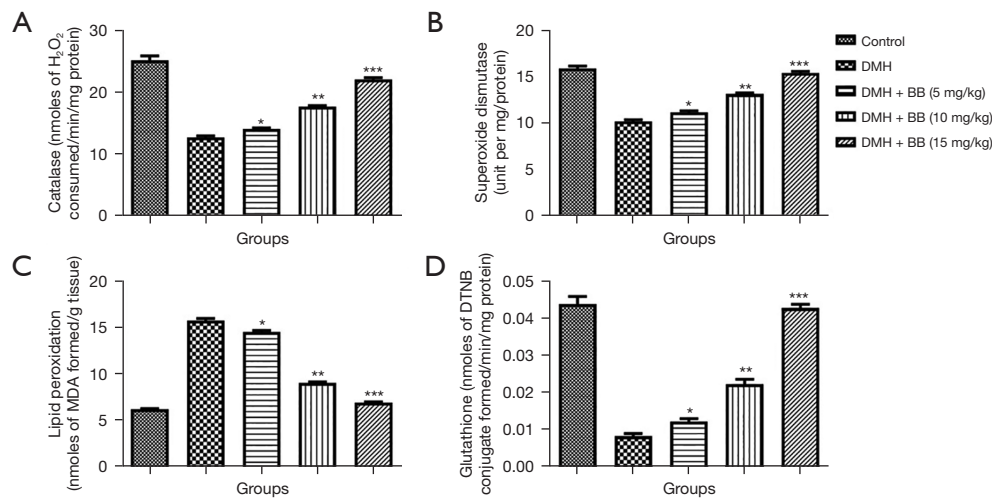


Figure 1 Effect of BB on the antioxidant parameters of DMH induced CRC in rats. (A) Catalase; (B) superoxide dismutase; (C) lipid peroxidation; and (D) glutathione. All data denote mean \pm SEM of six animals per group. Data obtained are significantly different from the DMH treated group (* $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$). DMH, 1,2-dimethylhydrazine; CRC, colorectal cancer; BB, boeravinone B.

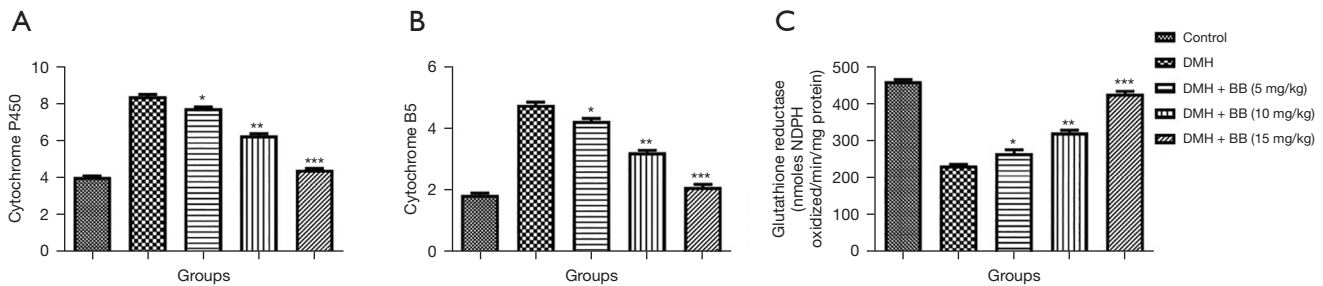


Figure 2 Effect of BB on the phase I enzymes of DMH induced CRC in rats. (A) Cytochrome P450; (B) cytochrome B5; and (C) glutathione reductase. All data denote mean \pm SEM of six animals per group. Data obtained are significantly different from the DMH treated group (* $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$). DMH, 1,2-dimethylhydrazine; CRC, colorectal cancer; BB, boeravinone B.

($P < 0.001$) altered levels of cytokines, and BB (15 mg/kg) almost restored these normal (Figure 4).

MPO

MPO levels are usually boosted during cancer, and this was observed in DMH group rats. BB treated group rats showed significantly ($P < 0.001$) reduced levels of MPO, with BB (15 mg/kg) suppressing the level to near normal (Figure 5).

Inflammatory mediators

The inflammatory reaction plays a crucial role in the

expansion of cancer. In this study, DMH induced CRC rats exhibited boosted levels of COX-2 (Figure 6A), PGE₂ (Figure 6B), and iNOS (Figure 6C), while BB treated rats showed a significant ($P < 0.001$) suppression of inflammatory parameter levels. BB (15 mg/kg) treated rats exhibited the maximum reduction in the level of inflammatory parameters.

mRNA expression

DMH induced CRC rats exhibited boosted mRNA expression of GDI2, and BB treated rats significantly ($P < 0.001$) suppressed mRNA expression (Figure 7).

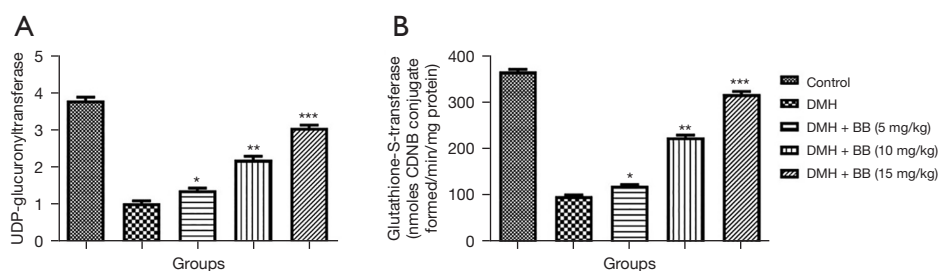


Figure 3 Effect of BB on the phase II enzymes of DMH induced CRC in rats. (A) UDP-glucuronyltransferase and (B) glutathione-S-transferase. All data denote mean \pm SEM of six animals per group. Data obtained are significantly different from the DMH treated group (* $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$). DMH, 1,2-dimethylhydrazine; CRC, colorectal cancer; BB, boeravinone B.

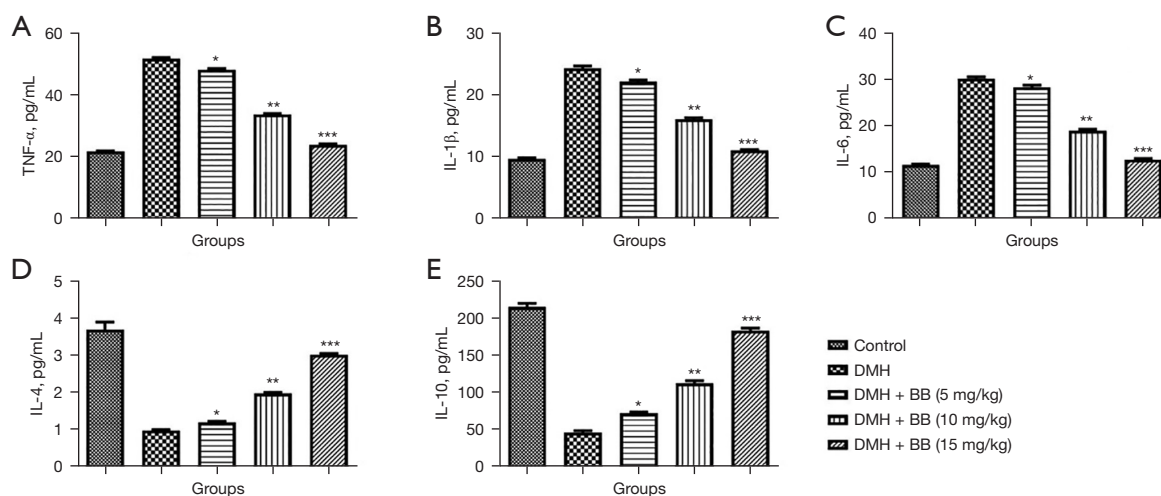


Figure 4 Effect of BB on the inflammatory cytokines of DMH induced CRC in rats. (A) TNF- α ; (B) IL-1 β ; (C) IL-6; (D) IL-4; and (E) IL-10. All data denote mean \pm SEM of six animals per group. Data obtained are significantly different from the DMH treated group (* $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$). DMH, 1,2-dimethylhydrazine; CRC, colorectal cancer; BB, boeravinone B; TNF- α , tumor necrosis factor- α ; IL-1 β , interleukin- β ; IL-4, interleukin-4; IL-6, interleukin-6; IL-10, interleukin-10.

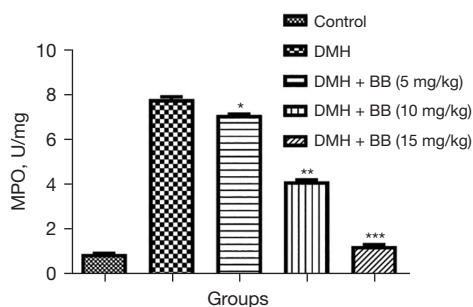


Figure 5 Effect of BB on the MPO activity of DMH induced CRC in rats. All data denote mean \pm SEM of six animals per group. Data obtained are significantly different from the DMH treated group (* $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$). DMH, 1,2-dimethylhydrazine; CRC, colorectal cancer; BB, boeravinone B; MPO, myeloperoxidase.

Discussion

Previous reports suggest the inflammatory reaction plays a crucial role in the expansion of CRC (22,23). Patients suffering from ulcerative colitis have a higher risk of progression of CRC, and immune cells infiltration generates different types of inflammatory cytokines and chemical factors, which boost the inflammatory reaction and enhance cell differentiation and proliferation (22,23). Chemotherapeutic agents are commonly used in the treatment of all types of the cancers, while plant-based drugs and their phytoconstituents exhibit protective effects with less side effects (4). Herbal drugs and their constituents are less toxic and more effective, and are commonly observed in various fruits, vegetables, and dietary agents

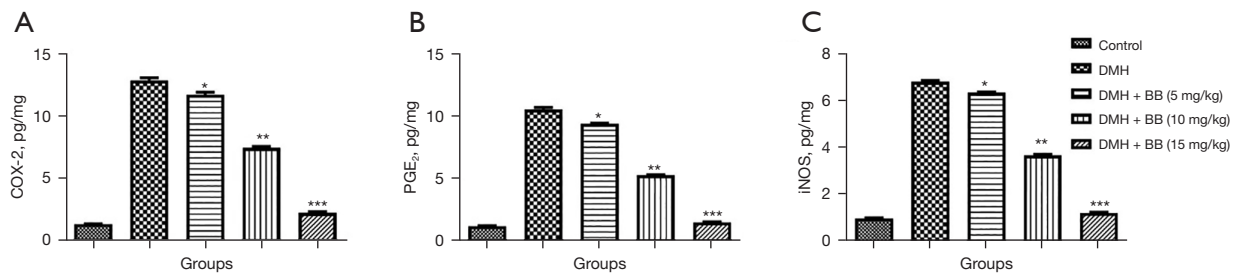


Figure 6 Effect of BB on the inflammatory parameters of DMH induced CRC in rats. (A) COX-2, (B) PGE₂, and (C) iNOS. All data denote mean ± SEM of six animals per group. Data obtained are significantly different from the DMH treated group (*P<0.05, **P<0.01 and ***P<0.001). DMH, 1,2-dimethylhydrazine; CRC, colorectal cancer; BB, boeravinone B; COX-2, cyclooxygenase-2; PGE₂, prostaglandin E₂; iNOS, inducible nitric oxide synthase.

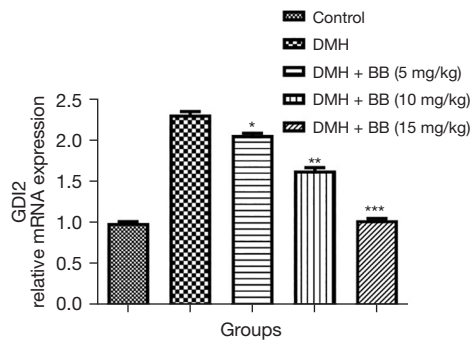


Figure 7 Effect of BB on the mRNA expression of DMH induced CRC in rats. All data denote mean ± SEM of six animals per group. Data obtained are significantly different from the DMH treated group (*P<0.05, **P<0.01 and ***P<0.001). DMH, 1,2-dimethylhydrazine; CRC, colorectal cancer; BB, boeravinone B.

(24,25). Phytoconstituents exhibit anti-inflammatory and antioxidant effect against various types of cancers such as renal, breast, hepatic, colorectal, and brain (22,26). Due to numerous effects of plant based phytoconstituents, in this experimental study, we scrutinized the chemoprotective effect of BB against DMH induced CRC in rats.

DMH is a potent carcinogen commonly used for the induction of CRC in rodent models. Previous research suggests the methyl diazonium ion boosts oxidative stress via methylation in the epithelial cells of colon tissue (2,27). Colon cancer follows exposure to carcinogens, and cells may then progress by a series of pre-cancerous lesions, premalignant, and malignant stages (1).

Oxidative stress plays a crucial role in the expansion and progression of gastrointestinal (GI) disease, ranging from chronic enteritis to CRC (1,9). Previous literature suggests oxidative induces inflammation, which further increases the

disease load in rodents and humans (1,27). In the rodent model, carcinogens cause the production of free radicals and induce oxidative stress, and the production of ROS can cause the peroxidation of lipids, which further induces cellular injury. As first line antioxidant enzymes, SOD and CAT play a crucial role in scavenging free radicals (28,29) and are involved in endogenous antioxidant mechanisms and protection of cells and tissues against free radicals like hydroxyl (OH) and superoxides (O₂). Both are also directly involved in the removal of ROS and act as the primary antioxidant enzymes (30). SOD and CAT are more sensitive to oxidative injury induced via the carcinogen (DMH) and are suppressed by its carcinogenic effect. The increase in free radical production exceeds the scavenging capacity of the endogenous antioxidant system during cancer (31,32). The production of LPO or MDA is one of the significant and appropriate markers of oxidative injury, and an increased level of LPO is found after DMH administration. Consistent with previous literature, our data exhibited a remarkable enhancement in LPO level after DMH administration, while BB treatment considerably suppressed it, suggesting an anticancer effect against CRC.

Enzymatic and non-enzymatic antioxidants are an important part of the body's defensive system against free radicals (3). GSH is a tripeptide (low molecular weight) cellular antioxidant which protects the lipid membrane from peroxidation via conjugating with the electrophile like 4-hydroxyl-3-nonenal (HNE), which is generated during lipid peroxidation and accordingly reduced during the conjugation reaction (33). GSH and its oxidized products are a major redox system of cells which interact with the -SH group in ROS and can be implicated in the enzymatic detoxification reaction for ROS as a cofactor or coenzyme (3,33). The level of GSH is suppressed in CRC, and BB

treatment can improve this, demonstrating its antioxidant effect.

DMH is a well-known alkylating agent that induces cellular DNA injury via forming an adduct. While some cells are repaired via DNA repair enzymes, some are not and undergo apoptotic removal (33). Apoptosis is a finely controlled process of cell death, in which caspase plays a crucial role (34,35). Previous research suggests caspases are cysteine dependent enzymes and are activated via oxidative stress (35,36). Caspase-3 is the main executioner caspase and is activated via extrinsic and intrinsic pathways. An increased level of caspase-3 induces the DNA fragmentation and cleavage of specific cellular protein such as lamins, PARP, and caspase during apoptosis (33). DMH induced CRC rats exhibited enhanced levels of caspase-3 and BB treatment considerably suppressed this.

The inflammatory reaction and oxidative stress play a crucial role in the progression and expansion of cancer, and inflammatory mediators such as COX-2 are significant markers, in colon cancer (3,33). In addition, enhanced COX-2 levels further induce colon injury and cause polyp formation, and research has targeted its chemoprotective effect. iNOS (a potent inflammatory marker) is also commonly boosted during cancer (3) and a similar result was observed in this study. DMH induced CRC group rats exhibited boosted levels of COX-2, iNOS, and PGE₂, and BB treatment considerably suppressed the level of COX-2.

Inflammatory cytokines, including TNF- α , play a crucial role in the initiation and progression of cancer (11,33). TNF- α is dependent on NF- κ B activation, which further boosts inflammation in tissue. In this study, DMH induced CRC group rats exhibited modulated levels of inflammatory cytokines, and BB treatment considerably altered these.

Previous reports show the expression of GDI2 is boosted in esophageal squamous cell carcinoma (37) and pancreatic cancer (38), suggesting it should be considered as a biomarker or potential molecular target for these cancers (15). A reduced expression of GDI2 is also observed in CRC, and it should be considered as a potential target for the treatment of this disease.

Conclusions

Our results suggest the oral administration of BB effectively diminishes the incidence of CRC and suppresses the progression of DMH induced CRC in rats. BB treatment considerably suppressed oxidative stress via altering the level of endogenous antioxidant parameters. The underlying

mechanism proposed suggests the chemoprotective effect of BB reduces oxidative stress and the inflammatory reaction, both of which play a crucial role in the expansion of CRC tumors in rodents. BB showed the protective effect against the DMH induced CRC in rats via suppression of inflammatory pathway.

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Footnote

Reporting Checklist: The authors have completed the ARRIVE reporting checklist. Available at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-733/rc>

Data Sharing Statement: Available at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-733/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-22-733/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Animal experiments were performed under a project license (Approval Number: GDY2102322) granted by ethics committee of The Affiliated Hospital of Guangdong Medical University, in compliance with The Affiliated Hospital of Guangdong Medical University guidelines for the care and use of animals.

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