RESEARCH PAPER

Effect Of Piperine On Oxidative Stress And Antioxidant Enzyme Status In Experimental Colorectal Carcinogenesis

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Abstract

Background: Colorectal cancer (crc) is a leading cause of cancer-related morbidity and mortality worldwide, with oxidative stress and inflammation playing critical roles in its pathogenesis. Piperine, a bioactive alkaloid derived from piper nigrum, has demonstrated antioxidant and anticancer properties in various experimental models.

Aim: The present study aimed to evaluate the effect of piperine on oxidative stress markers and antioxidant enzyme status in an azoxymethane (aom)/dextran sulphate sodium (dss)-induced experimental model of colorectal carcinogenesis.

Methods: Colorectal cancer was induced in swiss albino mice using aom/dss. Piperine was administered orally at doses of 50 and 100 mg/kg body weight, and its effects were compared with a standard chemotherapeutic agent, 5-fluorouracil (5-fu). Oxidative stress and antioxidant status were assessed by measuring malondialdehyde (mda), inducible nitric oxide synthase (inos), and antioxidant enzymes including superoxide dismutase (sod), catalase (cat), and glutathione peroxidase (gpx).

Results: The carcinogen-induced group exhibited significantly decreased activities of sod, cat, and gpx, along with elevated levels of mda and inos, indicating increased oxidative and inflammatory stress. Piperine treatment significantly restored antioxidant enzyme activities and reduced mda and inos levels in a dose-dependent manner. The effects observed were comparable to those of the standard drug 5-fu.

Conclusion: Piperine demonstrates significant antioxidant and anti-inflammatory effects in aom/dss-induced colorectal carcinogenesis by enhancing endogenous antioxidant defenses and reducing oxidative damage. These findings suggest that piperine holds promise as a potential chemopreventive and complementary therapeutic agent in colorectal cancer. Further studies are warranted to explore its molecular mechanisms and clinical applicability.

Keywords: Piperine, Colorectal Cancer, Oxidative Stress, Antioxidant Enzymes, Aom/Dss Model.

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INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the second leading cause of cancer-related mortality worldwide, representing a major public health concern (1). The pathogenesis of CRC is a complex, multistep process involving the accumulation of genetic and epigenetic alterations, chronic inflammation, and environmental factors that drive the transformation of normal colonic epithelium into malignant tissue (2,3). Oxidative stress has emerged as a critical contributor to colorectal carcinogenesis. It results from an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense system (4). Excessive ROS generation leads to damage of cellular macromolecules such as lipids, proteins, and DNA, thereby promoting tumour initiation and progression (5). Clinical and experimental evidence indicates that CRC patients exhibit significantly elevated levels of malondialdehyde (MDA), a marker of lipid peroxidation, along with reduced activities of antioxidant enzymes including superoxide dismutase

(SOD), catalase (CAT), and glutathione peroxidase (GPx) (6,7). Additionally, inducible nitric oxide synthase (iNOS), which produces nitric oxide during inflammatory conditions, is overexpressed in colorectal tumours, further linking oxidative and nitrosative stress with CRC development (8).

The azoxymethane (AOM)/dextran sulphate sodium (DSS) model is a well-established experimental system for studying colitis-associated colorectal carcinogenesis in rodents (9). This model closely mimics the inflammation-driven progression observed in human CRC and is widely used for evaluating chemopreventive and therapeutic interventions (10). In recent years, naturally derived bioactive compounds have gained increasing attention as potential alternatives or adjuncts to conventional cancer therapies due to their multi-targeted actions and relatively low toxicity (11). Piperine (1-piperoylpiperidine), the principal alkaloid found in black pepper (*Piper nigrum* L.) and long pepper (*Piper longum* L.), exhibits a wide range of pharmacological properties, including antioxidant, anti-inflammatory, immunomodulatory, and anticancer effects (12). In colorectal cancer, piperine has been shown to inhibit tumour cell proliferation by inducing G1 phase cell cycle arrest and apoptosis through mechanisms involving endoplasmic reticulum stress and modulation of PI3K/Akt and MAPK signalling pathways (13,14). It also suppresses the Wnt/β-catenin signalling pathway, which is dysregulated in the majority of CRC cases, highlighting its therapeutic relevance (15).

Furthermore, piperine has been reported to modulate the NF-κB/Nrf2/Keap1/HO-1 signalling axis, a key regulatory pathway linking inflammation and oxidative stress in carcinogenesis (16). Recent studies suggest that piperine can induce autophagy in colon cancer cells via modulation of AKT/mTOR signalling and ROS generation (17). In addition, piperine enhances the bioavailability and therapeutic efficacy of conventional anticancer drugs, supporting its potential role in combination therapy (18,19). Despite these promising findings, the in vivo effects of piperine on oxidative stress biomarkers and antioxidant defense systems in colorectal carcinogenesis remain insufficiently explored. Therefore, the present study was designed to evaluate the effect of piperine on oxidative stress markers (MDA and iNOS) and antioxidant enzymes (SOD, CAT, and GPx) in an AOM/DSS-induced colorectal cancer model.

MATERIALS AND METHODS

Reagents and Chemicals

Piperine, Azoxymethane (AOM), Dextran Sulphate Sodium (DSS) and 5- Fluorouracil (5-FU) were purchased from Sigma Alderich chemical sciences company, India.

Animals

In this study, 6-8 weeks-old Swiss albino mice (n=4) weighing 60-80g were used, which was procured from Laboratory Animal Medicine, Centre for Animal Health Studies, Tamil Nadu Veterinary & Animal Sciences University (TANUVAS), Chennai - 600 051, Tamil Nadu. The standard environment and food condition were provided to all the animals and were maintained at 45–55% relative humidity and temperature of 24 ± 3ºC with 12h of light / 12h of dark cycle along with free access to water and standard diet. The experiments were performed according to CPCSEA guidelines (IAEC approval No: BRLULAC/SDCH/SIMATS/IAEC/802021/077).

Blood and tissue collection

After 10 weeks animals were anesthetized with Ketamine (50–100 mg/kg) and Xylazine (5–10 mg/kg), and blood was collected from the retro-orbital plexus and serum was separated for examination of biochemical and ELISA analysis. The colon samples were collected and washed with normal saline and treated with phosphate buffer saline for analysis of antioxidants and biomarkers.

Assessment of antioxidant biomarkers - SOD (Superoxide Dismutase), CAT (Catalase), and GPx (Glutathione Peroxidase)

Serum levels of antioxidant enzymes SOD, CAT, and GPx were quantified using commercially available sandwich ELISA kits according to the manufacturer's instructions. Briefly, standards and samples were added to antibody-coated microplate wells and incubated for specific antigen binding. After washing, HRP-conjugated detection antibodies were added, followed by substrate solution to develop color. The reaction was stopped, and absorbance was measured at 450 nm using a microplate reader, and enzyme levels were calculated from standard calibration curves.

Assessment of oxidative stress markers - MDA (Malondialdehyde) and iNOS (Inducible Nitric Oxide Synthase)

Serum levels of iNOS and MDA were measured using ELISA kits as per the manufacturer's protocol. Samples and standards were added to pre-coated wells and incubated to allow antigen–antibody interaction (competitive ELISA for MDA where applicable). After washing, enzyme-linked secondary antibody and chromogenic substrate were added for color development. Absorbance was recorded at 450 nm, and concentrations were determined using respective standard curves.

STATISTICAL ANALYSIS

Data was subjected to statistical analysis using one-way analysis of variance and Duncan's multiple range test to assess the significance of individual variations between the control and treatment groups using a computer- based software (SPSS 23 for Windows student version) and expressed as mean + standard error of the mean. In Duncan's test, the significance was considered at the level of $p < 0.05$.

RESULTS

Effects of Piperine on antioxidant enzymes

The activities of antioxidant enzymes (SOD, CAT, and GPx) were markedly reduced in the CRC-induced group (SOD - 11 p/mL, CAT - 5 ng/mL, GPx - 14 pmol/L) compared to the normal control group (SOD - 20 p/mL, CAT - 18 ng/mL, GPx - 30 pmol/L), indicating severe oxidative stress. Treatment with piperine significantly restored these enzyme levels, with 50 mg/kg showing moderate improvement (SOD - 17 p/mL, CAT -10 ng/mL, GPx - 22 pmol/L) and 100 mg/kg showing further enhancement (SOD -18 p/mL, CAT -15 ng/mL, GPx- 25 pmol/L). The effect was comparable to the standard drug 5-FU group (SOD -21 p/mL, CAT -17 ng/mL, GPx - 29 pmol/L), indicating that piperine effectively restores antioxidant defense systems in AOM-induced colorectal carcinogenesis.

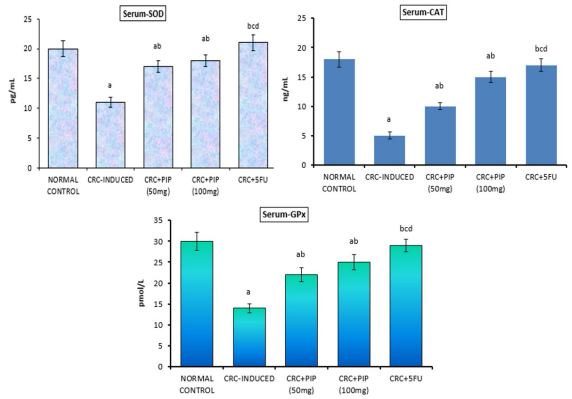

Figure 1: Piperine exhibits its antioxidant property by enhancing the antioxidant enzyme activity. AOM induced colon carcinogen group shows lowered activity of SOD, CAT and GPx enzymes than compared to normal and treated groups. Both 50 and 100 mg/kg b.w.t of Piperine shows significantly higher levels of these antioxidant enzymes as compared to carcinogen group.

Effect of Piperine on lipid peroxidation – MDA biomarker

Serum MDA levels were significantly elevated in the CRC-induced group (app. 7 nmol/L) compared to the normal control group (app. 2 nmol/L), reflecting increased lipid peroxidation and oxidative damage. Piperine treatment reduced MDA levels in a dose-dependent manner, with values of approximately 5 nmol/L at 50 mg/kg and 4 nmol/L at 100 mg/kg. The reduction was more pronounced in the 5-FU-treated group (app. 3 nmol/L). These findings indicate that piperine effectively attenuates lipid peroxidation and protects against oxidative membrane damage.

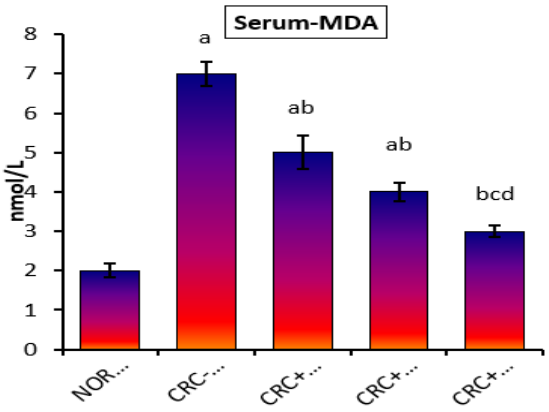

Figure 2: Piperine alleviates the MDA levels. AOM induced cancer group displayed elevated levels of MDA than compared to normal, standard drug and Piperine treated groups. Piperine effectively reduces MDA levels exhibiting its protective action against lipid peroxidation.

Effect of Piperine on oxidative stress marker – iNOS biomarker

The level of iNOS was significantly elevated in the CRC-induced group (app. 9 ng/mL) compared to the normal control group (app. 5 ng/mL), indicating increased inflammatory and nitrosative stress. Piperine treatment reduced iNOS levels to approximately 6 ng/mL at both 50 mg/kg and 100 mg/kg doses, demonstrating its anti-inflammatory potential. The standard drug 5-FU showed a greater reduction (app. 4.5 ng/mL), approaching normal levels. These results suggest that piperine suppresses inflammation

associated with colorectal carcinogenesis by downregulating iNOS expression.

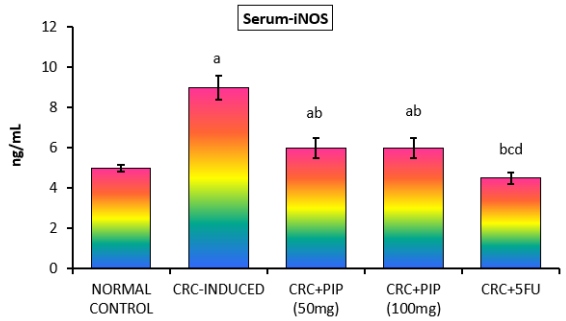

Figure 3: Piperine exhibits anti-inflammatory property. iNOS, an inflammatory marker was high in carcinogen group. Piperine reduced inflammation in AOM induced CRC models remarked by lowered levels of iNOS when compared to carcinogen group which shows higher concentration of iNOS.

DISCUSSION

The present study investigated the effect of piperine on oxidative stress markers and antioxidant enzyme status in an AOM/DSS-induced model of colorectal carcinogenesis. The findings clearly demonstrate that piperine treatment significantly enhanced the activities of key antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), while concurrently reducing the levels of malondialdehyde (MDA) and inducible nitric oxide synthase (iNOS) compared to the carcinogen control group. These results collectively indicate that piperine exerts a protective effect by restoring redox balance and mitigating oxidative and nitrosative stress during colorectal cancer progression. Oxidative stress is widely recognized as a major driving factor in colorectal carcinogenesis. An imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defense system results in oxidative damage to lipids, proteins, and DNA, thereby promoting tumour initiation and progression (20,21). In the present study, the AOM/DSS-induced group exhibited a marked decline in SOD, CAT, and GPx activities compared to the normal control group, consistent with previous reports in colorectal cancer models (22). The observed depletion of these enzymes may be attributed to their excessive utilization in neutralizing elevated ROS levels generated during carcinogenesis.

Administration of piperine at doses of 50 and 100 mg/kg significantly restored the activities of SOD, CAT, and GPx, highlighting its role in strengthening the endogenous antioxidant defense system. These enzymes function synergistically to detoxify reactive species: SOD converts superoxide radicals into hydrogen peroxide, CAT decomposes hydrogen peroxide into water and oxygen, and GPx reduces hydrogen peroxide and lipid hydroperoxides using glutathione. The enhancement of these enzymatic defenses by piperine is in agreement with earlier findings by Selvendiran et al. (2003), who reported increased antioxidant enzyme activities in benzo[a]pyrene-induced lung carcinogenesis (23). Similarly, Safarbalou et al. (2023) demonstrated that piperine reduced oxidative stress markers in radiation-induced colon injury (24), while Adeyemo et al. (2021) showed restoration of antioxidant status in toxin-induced hepatic damage (25). Collectively, these findings support the potent antioxidant capability of piperine across different experimental models.

At the molecular level, the antioxidant effects of piperine are largely attributed to its regulation of the Nrf-2/Keap1/HO-1 signalling pathway. Piperine promotes the activation and nuclear translocation of Nrf-2, leading to the upregulation of antioxidant response element (ARE)-dependent genes encoding detoxifying and antioxidant enzymes (26). Furthermore, Ghasemi et al. (2025) highlighted that piperine modulates multiple signalling pathways, including PI3K/Akt/mTOR and ERK1/2, thereby contributing to its broad-spectrum antioxidant and anticancer effects (27). Malondialdehyde (MDA), a well-established biomarker of lipid peroxidation, was significantly elevated in the carcinogen-induced group, reflecting increased oxidative damage to cellular membranes. This observation is consistent with clinical findings in colorectal cancer patients (20). Piperine treatment significantly reduced MDA levels, indicating its ability to inhibit lipid peroxidation. Similar reductions in MDA have been reported by Mohammadi et al. (2019) in ischemia-reperfusion injury models (28). The decrease in MDA levels may be attributed to both the direct free radical scavenging activity of piperine and its indirect effect through enhancement of antioxidant enzymes (29).

The present study also demonstrated a significant increase in iNOS levels in the carcinogen group, indicating enhanced inflammatory and nitrosative stress. Overexpression of iNOS leads to excessive nitric oxide production, which contributes to DNA damage and tumour progression. Piperine treatment significantly reduced iNOS levels, suggesting strong anti-inflammatory activity. This finding is supported by previous studies showing that piperine suppresses

iNOS expression and nitric oxide production in inflammatory models (30-32). Additionally, Gholijani et al. (2025) reported that piperine inhibits pro-inflammatory macrophage polarization, further supporting its role in modulating inflammatory responses. Mechanistically, the anti-inflammatory effects of piperine are closely linked to inhibition of the NF-κB signalling pathway. NF-κB regulates the expression of various pro-inflammatory mediators, including iNOS, COX-2, TNF-α, and interleukins. Piperine inhibits NF-κB activation by preventing IκBα degradation and blocking nuclear translocation of the p65 subunit, thereby suppressing downstream inflammatory gene expression. This mechanism is particularly important in colorectal carcinogenesis, where oxidative stress and inflammation form a reinforcing cycle that promotes tumour development (33).

Recent studies have further elucidated the anticancer potential of piperine in colorectal cancer. Chang et al. (2025) demonstrated that piperine induces apoptosis and G1 phase cell cycle arrest in colorectal cancer cell lines through modulation of oxidative stress and key signalling pathways (34). Similarly, Xia et al. (2024) reported that piperine induces autophagy via regulation of AKT/mTOR signalling and ROS generation (35). Chidananda et al. (2025) further emphasized piperine's ability to target multiple oncogenic pathways, including Wnt/β-catenin and STAT3 signalling, thereby inhibiting tumour growth and metastasis. The dose-dependent effects observed in the present study, where both 50 and 100 mg/kg doses were effective, are consistent with previous *in vivo* studies. Notably, the effects of piperine were comparable to those of the standard chemotherapeutic agent 5-fluorouracil, highlighting its potential as a complementary therapeutic agent (36). Additionally, piperine is known to enhance drug bioavailability by inhibiting drug-metabolizing enzymes and efflux transporters, which may further improve the efficacy of combination therapies (37). The present study demonstrates that piperine exerts significant protective effects against oxidative stress and inflammation in AOM/DSS-induced colorectal carcinogenesis. These effects are mediated through enhancement of antioxidant enzymes, reduction of lipid peroxidation, and suppression of iNOS-mediated inflammation, likely via modulation of Nrf-2 and NF-κB signalling pathways.

CONCLUSION

The present study demonstrates that piperine exerts significant protective effects against AOM/DSS-induced colorectal carcinogenesis by modulating oxidative stress and inflammation. Piperine treatment enhanced the activities of antioxidant enzymes (SOD, CAT, and GPx), indicating improved cellular defense mechanisms. It also significantly reduced malondialdehyde (MDA) levels, suggesting inhibition of lipid peroxidation. Additionally, piperine suppressed inducible nitric oxide synthase (iNOS), reflecting its anti-inflammatory potential. These effects may be mediated through modulation of Nrf-2/Keap1/HO-1 and NF-κB signalling pathways. The comparable efficacy with 5-fluorouracil highlights its promise as a complementary therapeutic agent. Further studies focusing on molecular mechanisms, safety, and clinical validation are required to establish piperine as a potential chemopreventive agent in colorectal cancer.

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