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BIOCHEMICAL INFLUENCE OF *FICUS EXASPERATA* ON THE COLON OF HEALTHY WISTAR RATS AND ITS APOPTOTIC EFFECTS ON COLORECTAL CANCER

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ABSTRACT

Dysregulation of the apoptotic pathway is one of the hallmarks of colorectal cancer progression. Apoptosis is a programmed cell death that occurs during normal development and aging. It is genetically regulated and involves intrinsic and extrinsic pathways. This study investigates how the methanol leaf extract of *Ficus exasperata* could promote apoptosis in colorectal cancer, and also the effect on colon antioxidant status of apparently healthy Wistar rats. This study was done in three phases. In the first phase, the acute toxicity check of the extract was done using a total of 12 rats. In phase 2, sub-chronic test was carried out with a total of 20 rats divided into four groups. 48 rats with 6 rats in each group were used in the third phase of this study. The third phase investigates the effect of the extract on some apoptotic genes. The oral toxicity test showed that the plant is not toxic to the animals as reflected in the antioxidant status and lipid peroxidation marker. This claim was further supported by the histology result. BAX, BCL2 and TP-53 were the apoptotic genes that were assayed for in this study. BCL-2 an antiapoptotic gene was found to be high in the group that took the carcinogen without treatment. The proapoptotic genes TP53 and BAX were significantly low in this group as well but the extract was able to mitigate the effect of the carcinogen hence, an increase in the relative gene expression of this proapoptotic gene in treated groups.

Keywords: Toxicity, Antioxidant, Apoptosis, Colorectal cancer, *Ficus exasperata*

INTRODUCTION

Deregulation of apoptosis, a fundamental process of programmed cell death, is a hallmark of human cancer and contributes to therapeutic resistance in colorectal cancer (Xie *et al*., 2020: Xu *et al*., 2020). In colorectal cancer, an imbalance occurs between cell division, cell death, and cells that should have undergone apoptosis but did not receive the signals to do so (Chun *et al*., 2013). Various biochemical changes characterize apoptosis; disrupting the balance of pro-apoptotic and anti-apoptotic proteins (Wong, 2011). The regulation of cell death hinges not on the absolute quantity of proteins but on the critical ratio between pro-apoptotic (Bax, Bak, Bok/Mtd) and anti-apoptotic proteins (Bcl-2, Bcl-xL, Mcl-1, Bcl-w, A1/Bfl-1, and Bcl-B/Bcl2L10), exerting a significant influence on apoptosis (Hassan *et al*., 2023). Dysregulation, often observed in cancer, involves the over- or under-expression of certain genes and their resultant regulatory proteins, contributing to reduced apoptosis in cancer cells (Gavathiotis *et al*., 2009; Ghibelli and Diederich, 2010; Doerflinger *et al*., 2015). As with other types of cancer, the underlying mechanism of colorectal cancer pathogenicity is associated with the uncontrolled proliferation of cells, activation of proto-oncogenes and inactivation of tumor suppressor genes (Yin *et al*., 2018). The p53 protein, also known as tumor protein 53 (TP53), is a well-known tumor suppressor encoded by the TP53 gene located on chromosome 17 (17p13.1) (Joruiz and Bourdon, 2016; Vieler and Sanyal, 2018). This guardian of the genome, weighing 53 kDa, plays a multifaceted role in apoptosis induction, cell cycle regulation, development, differentiation, gene amplification, DNA recombination, chromosomal segregation, and cellular senescence (Liebl and Hofmann, 2021). Defects in the p53 tumor suppressor gene are implicated in colorectal cancer (Li *et al*., 2019).

Ficus exasperata Vahl, commonly called sandpaper plant, belongs to the Moraceae Family (Odunbaku *et al*., 2008). The plant has been ethnobotanically reported to have several therapeutic uses (Akinjogunla and Fatunla, 2017; Olude and Emeninwa, 2025). Reports of Buniyamin *et al*. (2007) and Lawal *et al*. (2009) clearly showed that this plant can be used in the treatment and management of hypertension, arthritis, and epilepsy. The plant was also used in the treatment of some other ailments; ulcers, intestinal pain, cough and, haemorrhoids ulcer (Odunbaku *et al*., 2008; Sonibare *et al*., 2006; Adebayo *et al*., 2009).

However, not much has been reported about the ethnomedicinal benefits of *Ficus exasperata* on colon antioxidant status and its apoptotic functions in colorectal cancer. In this experiment, the possible influence of *Ficus exasperata* on the colon profile of healthy adult Wistar rats was investigated by assaying some basal biochemical parameters, the study went further to investigate the effect of this plant on apoptosis in colorectal cancer.

MATERIALS AND METHODS

Plant Collection, Identification and Preparation

The leaves of *Ficus exasperata* were plucked from a local garden in Benin City, Edo State, Nigeria. The leaves were verified by Prof. H. Akinnibosun in the Department of Plant Biology and Biotechnology, University of Benin, Benin City, Edo State, Nigeria. The leaves after properly air-dried and pulverized were soaked in methanol for 72 hours with constant stirring. After the stipulated time it was sieved, and subjected to freeze-drying. The powdered extract was kept in an airtight container and kept at 4°C in a refrigerator.

Preparation of 1,2-dimethyl hydrazine (DMH)

The carcinogen used for the induction of colorectal cancer was DMH. Freshly prepared DMH solution was used for each administration. The carcinogen was dissolved in 1 mM EDTA, and 1 M sodium hydroxide was used to achieve pH 6.5. Twice a week, the carcinogen was subcutaneously injected at a dose of 40 mg/kg body weight. (Chari *et al*., 2018).

Experimental Design

Acute toxicity study

For the acute toxicity test, Lorke's method (1983) was followed using 12 healthy male Wistar rats. The test comprised two phases. In Phase 1, nine rats were divided into three groups (three rats each) and administered different doses (10, 100, and 1000mg/kg) of methanol extract from *F. exasperata* leaves. The rats were observed for 24 hours to monitor behaviour and mortality. Phase 2 involved three rats distributed into three groups (one rat each), administered higher doses (1600, 2900, and 5000mg/kg) of the methanol extract. These rats were observed for 24 hours for changes in behaviour and mortality. The extracts were administered using a gavage.

Sub-chronic toxicity test

In the repeated dose oral toxicity study following the Organization for Economic Co-operation and Development (OECD) guideline 407, 24 animals were divided into four groups of six animals each. Group 1 served as a control, while Groups 2, 3, and 4 received extract doses of 125, 250, and 500mg/kg body weight, respectively, for 28 days. Daily evaluations included monitoring mortality, body weights, feed, and water consumption, as well as general toxicity signs. After the 28-day period, the animals were sacrificed. The colon was excised and washed in ice-cold saline, and some portions were preserved in 10% formalin for histopathology. The remaining tissues were homogenized in normal saline, centrifuged, and the obtained supernatant was used for enzyme activity assays. Written approval for the study was obtained from the Research Ethics Committee Guideline Principles on Handling of Animals of the Faculty of Life Sciences, University of Benin, and was strictly adhered to

Assays

Malondialdehyde (MDA) levels were estimated by the method of Burge and Aust (1978). Total protein (TP) was determined using lowry's method, (1951) and catalase (CAT) was assayed according to the method of Cohen et al., (1970). Superoxide dismutase (SOD) was determined according to the method of Misra and Fridovich (1972). Glutathione Peroxidase (GPx) was determined according to the method of Paglia and Valentine, (1969) and reduced glutathione (GSH) was estimated according to the method of Ellman (1959).

Histopathological Evaluation

Tissue fixation followed Kiernan's method (2008): colon tissue was fixed in 10% buffered formalin, dehydrated, and paraffin-embedded. Sections were obtained, mounted on slides, and haematoxylin-eosin stained for light microscopic examination. Slides were coded and analyzed by a histopathologist.

Statistical Analysis of Data

The obtained data underwent statistical analysis, with values presented as Mean ± Standard error of mean. Comparisons between samples were conducted using ANOVA, Tukey's multiple comparison test (SPSS, version 17), and GraphPad Prism. Significance was determined at p-values below 0.05 ($p<0.05$).

Phase 3 Design

Forty-eight (48) Wistar albino rats were used for this study. The experimental animals weighed between 150 and 200g and were divided into 8 groups, with six animals in each group.

Table 1: Experiment design

Group	Treatment
1	Feed + water
2	Extract (500mg/kg)
3	DMH only
4	DMH + extract (500mg/kg) for 12 weeks
5	DMH +extract (750mg/kg) for 12 weeks
6	Extract (500mg/kg) for four (4) weeks, then DMH for eight (8) weeks
7	DMH for eight (8) weeks, then extract (500mg/kg) for four (4) weeks
8	DMH + standard drug for 12 weeks

After 12 weeks, the animals were fasted overnight and sacrificed. The colon was excised and used for relative gene expression assay of BAX, BCL2 and TP53. Total RNA was extracted from tissue samples using the Quick-RNA MiniPrep™ Kit (Zymo Research). DNA contamination was eliminated through DNAse I treatment (NEB, Cat: M0303S). RNA concentration was determined at 260 nm, and purity was assessed at 260 nm and 280 nm using an A&E Spectrophotometer (A&E Lab. UK). One microgramme (1 µg) of DNA-free RNA underwent reverse transcriptase reaction with a cDNA synthesis kit based on ProtoScript II first-strand technology (New England BioLabs). The reaction occurred in three steps: 65 °C for 5 min, 42 °C for 1 h, and 80 °C for 5 min (Elekofehinti *et al*., 2020). Polymerase chain reaction (PCR) for gene amplification utilized OneTaqR2X Master Mix (NEB) with specific primers (Inqaba Biotec, Hatfield, South Africa). Normalization and quantification of gene expression were performed using the GAPDH gene and "ImageJ" software (Elekofehinti *et al*., 2020).

RESULTS AND DISCUSSION

Acute oral toxicity test

As shown in Table 2 all through the 24hrs no behavioral changes or mortality was recorded Higher dosage was administered in phase 2, though no mortality was recorded but the rats were extremely weak.

Table 2: Acute toxicity result of rats treated with different doses of methanol extract of *F. exasperata*

	Treatment (methanol extract of *F. exasperata* leaves (MEFE))	**Observation**
Phase 1		
Group 1 (3 rats)	10mg/kg body weight	These three groups had no behavioral changes and no mortality was recorded within 24 hours of administration.
Group 2 (3 rats)	100mg/kg body weight	
Group 3 (3 rats)	1000mg/kg body weight	
Phase 2		
Group 1 (1 rat)	1600mg/kg body weight	The rats showed weakness, they became less active with disorganized movements but no mortality occurred within 24 hours of administration.
Group 2 (1 rat)	2900mg/kg body weight	
Group 3 (1 rat)	5000mg/kg body weight	

The findings align with Ufuoma *et al*. (2020), indicating that methanol leaf extract of *Ficus exasperata* (MEFE) exhibited no signs of toxicity at lower doses. However, higher doses led to symptoms such as unease, sluggishness, and dizziness, accompanied by decreased activity and disorganized movements. Importantly, no mortality occurred within 24 hours of administration (Adetuyi *et al*., 2022; Akinloye *et al*., 2025).

Sub-acute oral toxicity test

Tissue enzymatic antioxidants, total protein level, and lipid peroxidation marker (MDA) of the subacute toxicity study are presented in Table 3. Catalase (CAT), superoxide dismutase (SOD), glutathione activity (GSH), and glutathione peroxidase (GPx) activities in the colon showed no significant difference ($P>0.05$) across the groups. Lipid peroxidation marker (MDA) showed no significant difference across various groups in the colon but a decrease in this marker was seen in groups 2, 3, and 4 when compared with the control. Total protein (TP) showed no significant difference across the groups.

Table 3: Antioxidants, total protein and MDA levels of colon tissues

Assays	**GRP 1 (Control)**	**GRP 2 (125mg/kg bw extract)**	**GRP 3 (250mg/kg bw extract)**	**GRP 4 (500mg/kg bw extract)**
SOD (units/g wet tissue)	0.34 ± 0.04	0.29 ± 0.82	0.19 ± 0.04	0.26 ± 0.13
CAT (units/g wet tissue)	1.11 ± 0.44	5.88 ± 3.51	2.71 ± 1.38	2.25 ± 1.13
GPX (units/g wet tissue)	2.29 ± 0.3	3.19 ± 1.22	4.43 ± 1.11	4.79 ± 2.24
GSH (Mm/g tissue)	96.62 ± 13.28	127.79 ± 21.56	132.29 ± 27.39	91.66 ± 11.66
TP (g/dl)	5.77 ± 0.8	8.04 ± 2.99	11.2 ± 2.7	20.05 ± 9.39
MDA ($\times 10^{-4}$) mmol/g tissue	11.42 ± 3.99	7.8 ± 3.8	9.5 ± 1.73	6.2 ± 1.2

Values are expressed as mean ± SEM, n=6/group. Lowercase letters represent a significant difference at $P < 0.05$

The first line of defense of cells against oxidative damage is the antioxidant enzymes (Olude and Chukwu, 2023) and the main redox buffer in cells is GSH/GSSG (glutathione). Glutathione protects the thiols group of biomacromolecules and also helps eliminate reactive oxygen species (Adetuyi *et al*., 2022). Superoxide dismutase, CAT, and GPx are enzymatic antioxidants that maintain the antioxidant/prooxidant balance in biological cells (Ebhohon *et al*., 2024; Olude and Emeninwa, 2025). Superoxide dismutase catalyzes the dismutation of superoxide to hydrogen peroxide which is further broken down by catalase to water. Glutathione peroxidase also catalysis hydrogen peroxide to a less reactive substance (Olude and Omoregie, 2023). The doses of MEFE (125, 250, and 500mg/kg body weight) do not affect the colon tissue antioxidant which implies the extract is not toxic and did not elicit free radicals generation in this tissue. The lipid peroxidation marker (MDA) in this experiment also shows that the extract at various doses did not trigger oxidative stress. Lipid peroxidation damages tissue, disrupts the function and integrity of cell membranes and also overwhelms the antioxidant defense system (Adetuyi et al., 2022; Olude and Omoregie, 2024). Examining antioxidant enzymes in colon tissues, MEFE is not toxic to the colon.

Histology results of the effect of the plant extract on the colon

Plates 1 to 4 show the effect of the methanol extract of the plant on the colon tissue. The plant appeared non-toxic to the tissues even at 500mg/kg body weight. The normal architecture of the tissues was not tampered with. The colon tissue morphology was not distorted by the extract given to different groups. No microscopical changes were seen in the photomicrographs.

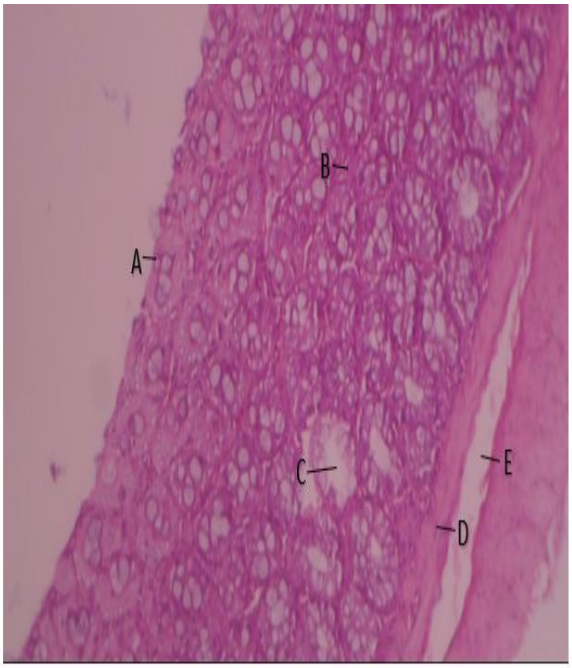

Plate 1: Rat intestine (control). Composed of normal tissue: A. mucosal lining, B. lamina propria, C. glands, D. muscularis mucosa, E. submucosa (H&E x 100)

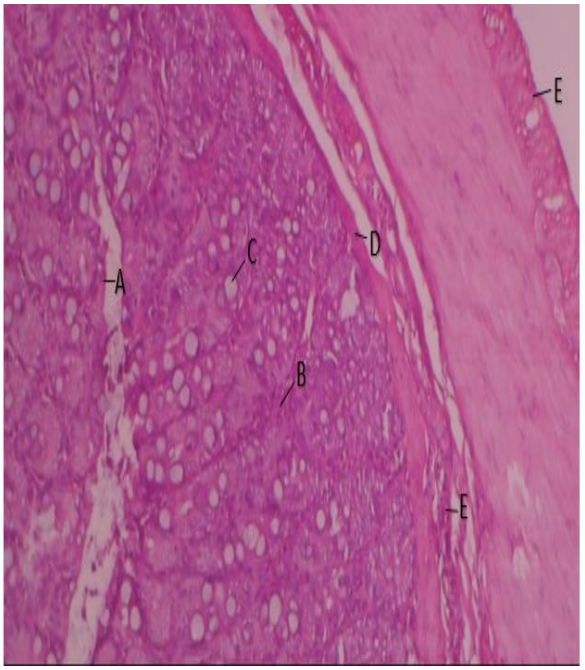

Plate 2: Colon section of rat given 125mg/kg bw extract showing normal architecture: A. mucosal epithelial lining, B. lamina propria, C. glands, D. muscularis mucosa, E. submucosa, F. muscularis propria (H&E x 100)

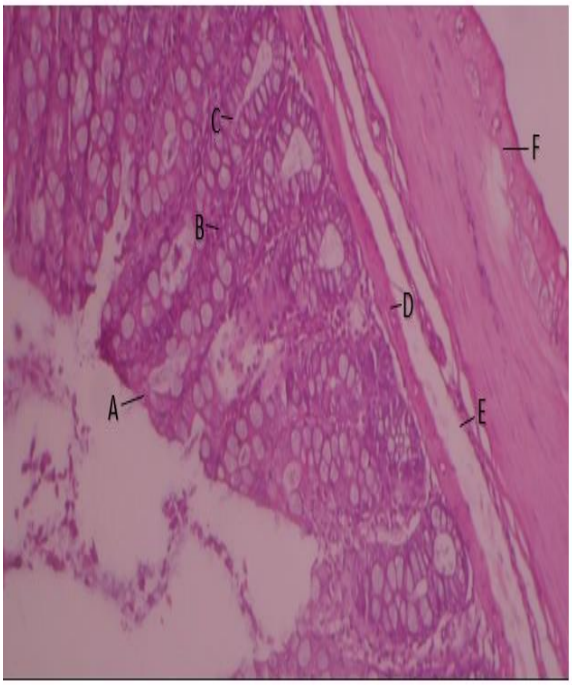

Plate 3: Colon section of rat given 250mg/kg b.w extract showing normal architecture: A. mucosal lining, B. lamina propria, C. glands, D. muscularis mucosa, E. submucosa, F. muscularis propria (H&E x 100)11q

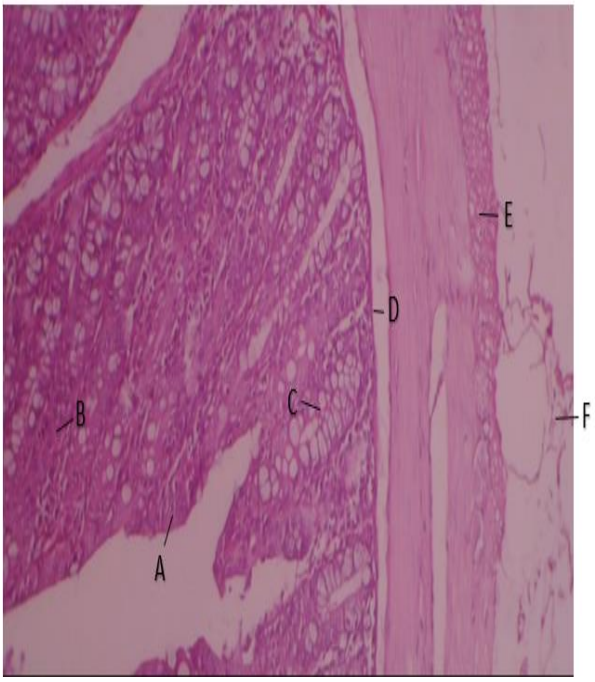

Plate 4: Colon section of rat given 500mg/kg b.w extract showing normal architecture: A. mucosal lining, B. lamina propria, C. glands, D. muscularis mucosa, E. muscularis propria, F. serosa (H&E x 100)

The non-alteration of enzyme levels in the tissue of rats administered low and moderate doses (125, 250, and 500 mg/kg bw) of the extract suggests that the extract did not pose any threat to the structural and functional integrity of the cells at these doses. This result was consistent with the histology results.

Effect of MEFE on apoptosis

Relative gene expression of TP53, BCL2, and BAX are represented in Figures 1-3. TP53, the guardian of the genome and BAX was statistically reduced ($P<0.05$ in group 3 (DMH only) compared to other treated groups. BCL2 the antiapoptotic gene was statistically increased ($P<0.05$) in all MEFE-treated groups compared with the DMH-only group.

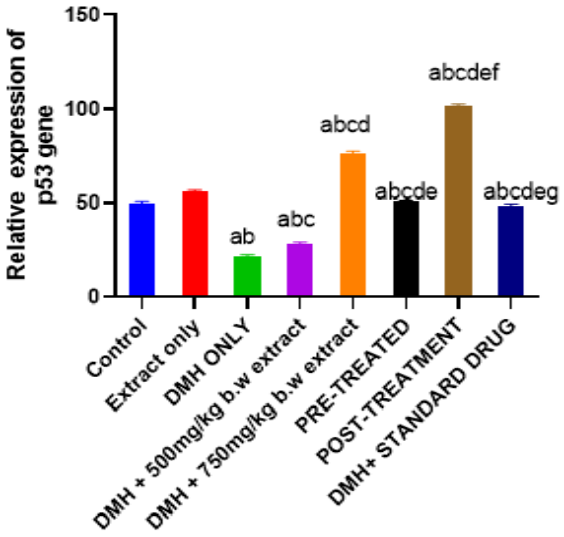

Figure 1: Relative expression of the p53 gene of rats in different groups. Values are expressed as mean ± SEM, n=6/ group Lowercase letters represent a significant difference at $P < 0.05$. The expression of this gene was more pronounced in group 7 compared to the other groups Values with a lowercase "a" denote a significant departure from standard control. It was statistically distinct from Extract only, as indicated by the local case letter "b". Values with the lowercase letter "c" denote significant differences from the DMH Only group. The lowercase letter "d" stands for a significant departure from co-treatment (DMH+ 500mg/kg MEFE). The lowercase letter "e" stands for a significant departure from co-treatment (DMH+ 750mg/kg MEFE). A statistically significant divergence from pre-treated and post-treated is denoted by the lowercase letters "f" and “g” respectively.

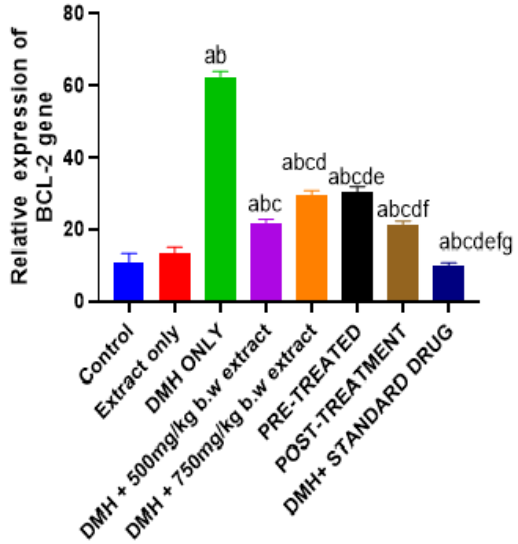

Figure 2: Relative expression of Bcl-2 gene of rats in different groups. Values are expressed as mean ± SEM, n=6/ group. Lowercase letters represent a significant difference at $P < 0.05$. B cell lymphoma gene-2 (Bcl-2) is an antiapoptotic marker. This gene was significantly expressed in group 3 compared to other groups ($P < 0.05$). MEFE-treated groups were able to reduce the gene expression of Bcl-2 hereby inducing apoptosis. Values with a lowercase "a" denote a significant departure from standard control. It was statistically distinct from Extract only, as indicated by the local case letter "b". Values with the lowercase letter "c" denote significant differences from the DMH Only group. The lowercase letter "d" stands for a significant departure from co-treatment (DMH+ 500mg/kg MEFE). The lowercase letter "e" stands for a significant departure from co-treatment (DMH+ 750mg/kg MEFE). A statistically significant divergence from pre-treated and post-treated is denoted by the lowercase letters "f" and “g” respectively.

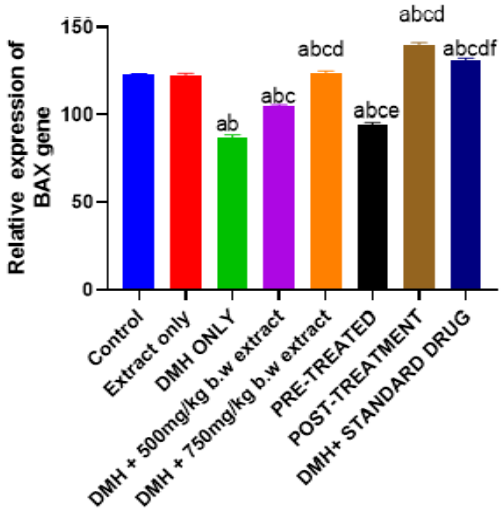

Figure 3: Relative expression of Bax gene of rats in different groups. Values are expressed as mean ± SEM, n=6/ group. Lowercase letters represent a significant difference at $P < 0.05$. A protein cognate of Bcl-2 with pro-apoptotic functions (Bcl-2 Homolog X; Bax). The molar ratio between Bax and the antiapoptotic Bcl-2 is the main molecular switch between apoptosis and survival. Group 6 BAX expression reduced significantly from all the treated groups. Group 5 and 7 had a BAX relative gene expression that was greatly increased compared to other groups. Values with a lowercase "a" denote a significant departure from standard control. It was statistically distinct from Extract only, as indicated by the local case letter "b". Values with the lowercase letter "c" denote significant differences from the DMH Only group. The lowercase letter "d" stands for a significant departure from co-treatment (DMH+ 500mg/kg MEFE). The lowercase letter "e" stands for a significant departure from co-treatment (DMH+ 750mg/kg MEFE). A statistically significant divergence from pre-treated and post-treated is denoted by the lowercase letters "f" and “g” respectively.

The loss of apoptosis in cancer cells is a critical event in cancer progression. Pro- and anti-apoptotic factor families control apoptosis. Pro-apoptotic (p53 and Bax) and anti-apoptotic genes (Bcl-2) are involved in cellular growth and apoptosis (Singh *et al*., 2015; Weyhenmeye *et al*., 2012). Cell growth, DNA damage repair, and apoptosis are all regulated by the p53 protein (Saddam *et al*., 2024). Relative expression of p53 and Bax gene was significantly decreased in group 3 compared with the groups that received the combination of both the carcinogen and plant extract. The p53 gene was more expressed in the group that received the highest dose of *F. exasperata*. but Bax gene was significantly increased in group 4. Thus, the induction of apoptosis, as evidenced by the elevated proapoptotic protein, p53 and Bax, may be involved in the mechanisms of the anticancer actions of this plant (Hassan *et al*., 2023).

Reports have shown an increase in the expression of an anti-apoptotic protein of the Bcl-2 family in DMH-induced carcinogenesis (Guo and Gao *et al*., 2022; Ghareeb *et al*., 2018). It triggers cellular proliferation and growth through the regulation of p53/Bcl2/Bax-mediated intrinsic apoptotic pathways. Relative gene expression of BCL-2 was significantly increased in the rats that received only the carcinogen. A drastic reduction in this gene expression was exhibited by the apoptotic properties embedded in *F. exasperata.*

CONCLUSION

The methanol extract of *F. exasperata* leaves is not toxic to colon tissues and this plant has great apoptotic initiation. The plant suppresses the anti-apoptotic gene which makes it a herbal remediation, pharmaceuticals, and nutraceuticals for colorectal cancer treatment.

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