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EFFECTS OF ACETONE AND METHANOL EXTRACTS OF *Zingiber officinale* (ROSCOE) ON SERUM CYCLOOXYGENASE-2 IN N,N'-DIMETHYLHYDRAZINE-INDUCED COLORECTAL CARCINOGENESIS IN WISTAR RATS

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ABSTRACT

Colorectal cancer (CRC) ranks among the leading causes of cancer death worldwide, and overexpression of cyclooxygenase-2 (COX-2) contributes substantially to its development. Because conventional COX inhibitors carry significant toxicity, plant-derived alternatives such as ginger (*Zingiber officinale*) are of interest. We compared acetone and methanol extracts of ginger rhizome for their capacity to lower serum COX-2 in Wistar rats with DMH-induced colorectal carcinogenesis, and measured the antioxidant capacity of each extract. Seventy-two adult male Wistar rats were divided into six groups (n = 12). Colorectal cancer was induced using DMH (20 mg/kg, subcutaneously, once weekly for 18 weeks). Animals received acetone or methanol ginger extracts (300mg/kg/body weight), administered daily by oral gavage for 21 weeks after completion of DMH induction, while the negative and positive control groups received no extract. Serum COX-2 was quantified by ELISA, and group differences were tested by one-way ANOVA followed by Tukey's test. The antioxidant capacity of each extract was determined with the Trolox equivalent antioxidant capacity (TEAC) and oxygen radical absorbance capacity (ORAC) assays. Intestinal tissues were examined macroscopically and colonic sections histologically (haematoxylin and eosin and methylene blue staining). DMH significantly increased COX-2 levels in the positive control group (41.35 ± 0.58 ng/mL) compared to the negative control. Treatment with acetone and methanol extracts significantly reduced COX-2 levels in cancer-induced rats (21.39 ± 0.12 and 20.67 ± 0.22 ng/mL, respectively; $p < 0.001$ versus positive control), and COX-2 in DMH-induced groups given the methanol extract did not differ significantly from the negative control. The methanol extract demonstrated higher antioxidant activity (TEAC: 73.02 ± 0.01; ORAC: 81,229.50 ± 1.94 µmol Trolox equivalents/100 g) compared to the acetone extract. DMH-induced groups showed intestinal inflammation, aberrant crypt foci and focal mild-to-moderate epithelial dysplasia on macroscopic and histopathological examination. Both acetone and methanol extracts of Zingiber officinale exhibit significant anti-inflammatory and antioxidant effects in DMH-induced colorectal cancer, suggesting that ginger is a potential supportive agent against DMH-induced inflammation.

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INTRODUCTION

Colorectal cancer (CRC) originates in the mucosal epithelium of the large intestine (colon) or rectum. GLOBOCAN estimated more than 1.9 million new diagnoses and roughly 900,000 deaths in 2020, about one in ten cancer deaths worldwide, with the highest incidence in Europe, Australia/New Zealand and North America [1]. Men carry a heavier burden. In the United States over 2015–2019, incidence in men exceeded that in women by about a third, and mortality by more than 40% [2]. CRC ranks third in both incidence and cancer mortality for each sex [3]. In Nigeria, CRC historically represented 3 to 6% of all malignant tumors, accounting for 10 to 50% of all gastrointestinal tract malignancies [4]. However, epidemiological data indicate a disturbing upward trend, with a rising number of cases reported from Ibadan over successive decades [5]. The peak incidence in Nigeria occurs between 42.9 and 53 years of age, roughly a decade earlier than in developed countries, with about three affected men for every two women [4,5].

Colorectal carcinogenesis is a multistep process often initiated by the transformation of benign adenomatous polyps into invasive malignancy. Hereditary syndromes, principally Lynch syndrome (hereditary nonpolyposis colorectal cancer, HNPCC) and familial adenomatous polyposis (FAP), account for approximately 5% of cases, and up to 30% of patients have a family history of the disease [6]. Environmental and lifestyle factors, including age, high red meat intake, low dietary fiber, obesity, sedentary lifestyle, smoking, and excess alcohol consumption, significantly modulate individual risk [7,8].

Overexpression of COX-2, the inducible isoform of the enzyme that converts arachidonic acid to prostaglandins, is central to CRC progression. It is detectable in about half of colorectal adenomas and in 80–90% of carcinomas, where it drives aberrant cell proliferation, suppresses apoptosis, promotes angiogenesis, and fosters an immunosuppressive tumor microenvironment [9,10]. Prostaglandin E2 (PGE2), the principal COX-2 product, acts through G-protein-coupled EP receptors to activate downstream oncogenic signaling cascades including the Ras/MAPK and PI3K/Akt pathways [11].

Inhibitors of COX and the resulting reduction of PGE2 synthesis are recognized as promising chemopreventive strategies for CRC, with epidemiological and clinical evidence demonstrating an approximately one-third reduction in CRC mortality with long-term aspirin use [12,13]. However, the prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with significant cardiovascular and gastrointestinal adverse effects, including peptic ulceration and increased thrombotic risk [14,15]. This toxicity burden necessitates the investigation of safer, naturally derived chemopreventive agents.

The increasing need for the development of mechanism-based anticancer therapeutic innovations also depends on rigorous appraisal of how well, and how safely, treatments perform in different cancers. Systematic reviews and meta-analyses offer a significant framework for incorporating available evidence and detecting clinically relevant therapeutic benefits and limitations, as demonstrated by recent evaluation of targeted antitumour therapy, including asciminib in chronic myeloid leukemia [16]. In parallel, preclinical investigation of naturally derived agents may offer important evidence towards their biological activity and potential treatment relevance in cancer therapeutic intervention and prevention.

The rhizome of ginger (*Zingiber officinale* Roscoe; Zingiberaceae) has a long history of use in traditional medicine as an anti-inflammatory, antimicrobial and antioxidant remedy. Its pungent phenolics (the gingerols, notably [6]-gingerol, together with shogaols, paradols and zingerone) act on both arms of arachidonic acid metabolism. They inhibit COX-1 and COX-2 as well as 5-lipoxygenase, limiting the synthesis of both prostaglandins and leukotrienes [17,18]. The dual inhibitory profile of ginger distinguishes it mechanistically from conventional NSAIDs and may confer a more favourable safety profile [17].

Preclinical evidence demonstrates that ginger root reduces tumour incidence and multiplicity in DMH-induced colon carcinogenesis in rats [19]. Ginger has also been shown to lower COX-1 protein expression in participants at increased risk for CRC [20], and to reduce gut tissue concentrations of PGE2 and 5-hydroxyeicosatetraenoic acid (5-HETE) in subjects at normal risk for CRC [21].

RAS signalling links COX-2 to CRC biology. Activating mutations in *KRAS* (about 40–45% of cases) and *NRAS* (2–6%) are among the most common genetic events in CRC [22,23]. They occur mainly at codons 12 and 13 of *KRAS* and codons 12, 13, 59 and 61 of *NRAS*, and they lock these small GTPases in the active state. This drives RAF/MEK/ERK and PI3K/Akt/mTOR signalling independently of upstream receptors [24]. PGE2 feeds into this circuit by transactivating the epidermal growth factor receptor (EGFR) through EP2 receptors [25,26], and RAS-mutant tumours do not respond to the anti-EGFR antibodies cetuximab and panitumumab [22,27]. The present study asked whether acetone and methanol extracts of ginger

rhizome lower serum COX-2 in Wistar rats with DMH-induced colorectal carcinogenesis, and how the antioxidant capacities of the two extracts compare

MATERIALS AND METHODS

Ethical Approval

In accordance with the guidelines for the use and care of experimental animals (National Institutes of Health Publication No. 80-23, National Academy of Sciences), this research was conducted with approval from the LAUTECH College of Health Sciences Ethical Committee, Osogbo, Nigeria (LAU/CHS/CS/CRE/005).

Plant Material Collection and Authentication

Fresh rhizomes of Zingiber officinale were purchased from a local market in Osogbo, Osun State, Nigeria. The rhizomes were selected based on their characteristic morphological features and cleaned thoroughly with distilled water before processing. The rhizomes were sliced, air-dried, pulverized into powder, and stored in airtight containers until extraction. A formal botanical authentication and voucher specimen deposition were not performed, and this has been acknowledged as a limitation of the study.

Preparation of Ginger Extracts

Two solvent-based crude extracts were prepared from the powdered ginger rhizomes using acetone and methanol as extraction solvents.

Acetone Extraction

Ten grams of powdered ginger rhizome were macerated in 100ml acetone in a clean glass container at room temperature [28]. The mixture was agitated intermittently and allowed to stand for a defined period of two weeks. After filtration through Whatman No. 1 paper, the solvent was concentrated on a Büchi Rotavapor R-210 (BÜCHI Labortechnik AG, Flawil, Switzerland) at 150 mbar in the Central Laboratory, Obafemi Awolowo University, Ile-Ife, Nigeria.

Methanol Extraction

The methanol extract was prepared in the same way, with 100 mL of methanol replacing acetone.

Storage of Extracts

The two extracts were separately stored in airtight amber containers at 4 °C until use.

Animals and Experimental Design

Seventy-two (72) adult male Wistar strain rats (eight weeks old) weighing 100 to 120 g were obtained and housed in standard stainless steel-roofed, plastic-bottomed cages at a controlled temperature of 25°C with a 12-hour light/dark cycle [19]. All animals had *ad libitum* access to standard rat chow and clean water. Bedding material composed of ground maize cob was replaced at least twice weekly. The rats were randomly divided into six groups of 12 animals each as described in Table 1.

Cancer Induction

Colorectal carcinogenesis was induced with N,N'-dimethylhydrazine dihydrochloride (DMH), a colon-specific procarcinogen. After hepatic conversion via azomethane, azoxymethane (AOM) and methylazoxymethanol (MAM), it yields the DNA-alkylating methyldiazonium ion [29]. Immediately before each injection, DMH was dissolved in 1 mL of ethylenediaminetetraacetic acid (EDTA) solution and brought to pH 6.5 with 1 mL of sodium bicarbonate to stabilise it. Groups B, D and F received DMH (20 mg/kg) by subcutaneous injection into the inguinal region once a week for 18 weeks [19,30].Faecal occult blood tests in DMH-induced groups became positive at week 15, indicating DMH-induced colonic mucosal injury. DMH injections were continued until week 18 to complete the induction protocol, after which administration of the ginger extracts commenced and continued once daily by oral gavage for 21 weeks, a treatment period consistent with that used in a previous evaluation of ginger against DMH-induced colorectal carcinogenesis in rats [31].

Faecal Occult Blood Test

Faecal occult blood testing (FOBT) was performed to assess the presence of occult gastrointestinal bleeding associated with N,N'-dimethylhydrazine (DMH)-induced colorectal lesions. Fresh faecal pellets were collected individually from each rat into clean, sterile containers at week 15 of DMH administration. The samples were analysed using a commercially available faecal occult blood test kit according to the manufacturer's instructions. Test results were recorded as positive or negative based on the appearance of the manufacturer's specified reaction and were used as an adjunct indicator of colorectal pathology during the induction phase, before extract administration began. Faecal testing has previously been used to monitor the progression of DMH-induced colonic lesions in rats [32].

Table 1. Experimental group design and treatment protocol

Group	*Treatment*	*Cancer Induction*	*Inference*
A	*Rats;* no treatment; no ginger extract	*No*	*Negative control*
B	*Rats;* DMH injection; no ginger extract	*Yes*	*Positive control*
C	*Rats;* acetone extract; no DMH	*No*	*Test*
D	*Rats;* acetone extract; DMH injection	*Yes*	*Test*
E	*Rats;* methanol extract; no DMH	*No*	*Test*
F	*Rats;* methanol extract; DMH injection	*Yes*	*Test*

DMH = N,N'-dimethylhydrazine dihydrochloride.

Dosage information

According to previous studies, the dosages of ginger were selected based on their toxicological and pharmacological properties. Oral ginger at 50 mg/kg body weight suppressed DMH-induced colon carcinogenesis in rats [19], and ginger given by gavage at doses of up to 2000 mg/kg/day for 35 days was well tolerated in rats [33]. A dose of 300 mg/kg body weight, within this efficacious and well-tolerated range, was therefore used in the present study.

Extraction Yield

The extraction yield percentage was determined using the following equation [21]:

Extraction yield (%) = (Weight of dried extract / Weight of powdered ginger) × 100

- 1.27 g of **dried methanolic extract was** obtained from 10 g ginger powder
- 0.98 g of **dried acetonic extract was** obtained from 10 g ginger powder

Therefore, the extraction yields for this study are:

- **Methanolic extract:** (1.27 ÷ 10) × 100 = **12.7%**
- **Acetonic extract:** (0.98 ÷ 10) × 100 = **9.8%**

Dosage Calculation and Ginger Extracts Administration

After solvent evaporation, the dried methanol and acetone extracts were reconstituted in 2% Tween 80 and properly vortexed to obtain a homogenous suspension immediately before administration. The extracts were administered orally once per day with the use of an oral gavage syringe fitted with a stainless-steel feeding needle.

The treatment dose for both the methanolic and acetonic extracts was **300 mg/kg body weight**. Individually, the amount of ginger extract required for each animal was calculated based on its body weight using the following equation:

Dose of extract (mg) = Body weight (kg) × 300 mg/kg body weight

Following a two-week acclimatization period, the experimental Wistar rats weighed between 120–140 g at the commencement of treatment. Hence, a rat with a weight of 120 g (0.12 kg) received 36 mg of the extract, a rat with 130 g (0.13 kg) body weight received 39 mg, and 42 mg was administered to a rat weighing 140 g (0.14 kg). The amount of the dried extract calculated was freshly dissolved or suspended in the respective vehicle to obtain an appropriate dosing concentration before oral administration.

Throughout the period of the study, the rats' body weights were measured at regular intervals, and accordingly, the dose administered was adjusted to maintain a constant dose of 300 mg/kg body weight. Also, to ensure the consistency and stability of the methanolic and acetonic extracts during the entire period of treatment, fresh dosing solutions were prepared every day.

Blood Sample Collection and COX-2 Assay

On completion of treatment, the animals were anaesthetised and blood was drawn by cardiac puncture with a 5 mL syringe into Eppendorf tubes.

Serum was separated by centrifugation (3,000 rpm, 10 min) and taken to the laboratory on ice. Serum COX-2 (ng/mL) concentration was determined with a validated Randox Enzyme-Linked Immunosorbent Assay (ELISA) kit. TEAC [34] and ORAC [35] assays were used to measure the antioxidant capacity of each extract and of unextracted ground ginger, which served as the reference sample.

Histological Examination

Histopathological evaluation of colonic tissue sections from selected groups was done through staining with Hematoxylin and Eosin (H&E). This was carried out to confirm tissue inflammation, cancer induction and assess histopathological changes. The tissue sections were viewed by light microscopy at ×10 for overall architecture of the tissue and ×40 for cellular details. It evaluated structures like glandular architecture, inflammatory cell infiltrates, necrosis, and signs of tumor growth or regression.

During necropsy, the small intestine, caecum, colon, rectum and mesenteric lymph nodes were inspected for gross distension, inflammation, haemorrhage, necrosis and nodal enlargement. Colonic tissues were embedded in paraffin, sectioned at 4 µm and stained with H & E, and the sections were assessed for inflammatory changes, epithelial integrity, architectural disruption, erosion, dysplasia and other pathological lesions. Aberrant crypt foci (ACF) were visualised by methylene blue staining of the colonic mucosa under a stereomicroscope [29].

Statistical Analysis

Results are reported as mean ± SEM. Serum COX-2 values across the six groups, and TEAC and ORAC values across the three samples, were each compared by one-way ANOVA, with Tukey's HSD test for pairwise contrasts. Table 2 compares each group with the negative control and Table 3 with the positive control. $P < 0.05$ was considered significant (*) and $p < 0.01$ highly significant (**). Antioxidant data were analysed in IBM SPSS Statistics 23.0. The COX-2 ANOVA and Tukey tests were computed in Python (SciPy 1.17) from group means, SEMs and n = 12 per group.

RESULTS

Effect of *Zingiber officinale* Extracts on Serum Cyclooxygenase-2 Concentration

Serum COX-2 results are shown in Tables 2 and 3 and Figure 1. Treatment had a significant overall effect on serum COX-2 (one-way ANOVA, $F(5, 66) = 982.8$, $p < 0.001$). DMH induction significantly increased serum COX-2 concentration in the positive control group compared with the negative control ($p < 0.001$). Treatment with both acetone and methanol extracts significantly reduced COX-2 concentrations in DMH-induced groups. Serum COX-2 in Group E (methanol extract alone) and Group F (DMH + methanol extract) was statistically indistinguishable from the negative control ($p = 0.99$ and $p = 0.73$), whereas those in Group C (acetone extract alone; $p < 0.001$) and Group D (DMH + acetone extract; $p = 0.019$) remained significantly higher.

Table 2: COX-2 concentrations relative to negative control (Group A)

Group	COX-2 (ng/mL)
Group D: Cancer + Acetone Extract	21.39 ± 0.12 *
Group F: Cancer + Methanol Extract	20.67 ± 0.22
Group C: Acetone Extract Only	21.85 ± 0.09 **
Group E: Methanol Extract Only	19.94 ± 0.16
Group B: Positive Control (Cancer Only)	41.35 ± 0.58 **
Group A: Negative Control	20.14 ± 0.01

Mean ± SEM, n = 12. *$p < 0.05$, **$p < 0.01$ vs Group A (Tukey's test)

Further comparison of the treatment groups with the positive control is presented in Table 3. All extract-treated groups (C, D, E and F) and the negative control showed significantly lower COX-2 concentrations than the positive control group ($p < 0.001$), indicating attenuation of the DMH-induced inflammatory response following administration of *Zingiber officinale* extracts.

Table 3. COX-2 concentrations relative to positive control (Group B)

Group	**COX-2 (ng/mL)**
Group D: Cancer + Acetone Extract	*21.39 ± 0.12* **
Group F: Cancer + Methanol Extract	*20.67 ± 0.22* **
Group C: Acetone Extract Only	*21.85 ± 0.09* **
Group E: Methanol Extract Only	*19.94 ± 0.16* **
Group A: Negative Control	*20.14 ± 0.01* **
Group B: Positive Control	*41.35 ± 0.58*

Mean ± SEM, n = 12. **p < 0.01 vs Group B (Tukey's test).

COX-2 was highest in the positive control (Group B: 41.35 ± 0.58 ng/mL), exceeding every other group ($p < 0.001$). The negative control group (Group A) showed a basal COX-2 level of 20.14 ± 0.01 ng/mL, which was significantly lower than that of Groups B, C and D, but did not differ significantly from Group E (methanol extract only, 19.94 ± 0.16 ng/mL) or Group F (DMH + methanol extract, 20.67 ± 0.22 ng/mL). Treatment with the acetone extract in cancer-induced rats (Group D: 21.39 ± 0.12 ng/mL) and the methanol extract in cancer-induced rats (Group F: 20.67 ± 0.22 ng/mL) both significantly reduced COX-2 concentrations compared with the positive control ($p < 0.001$).

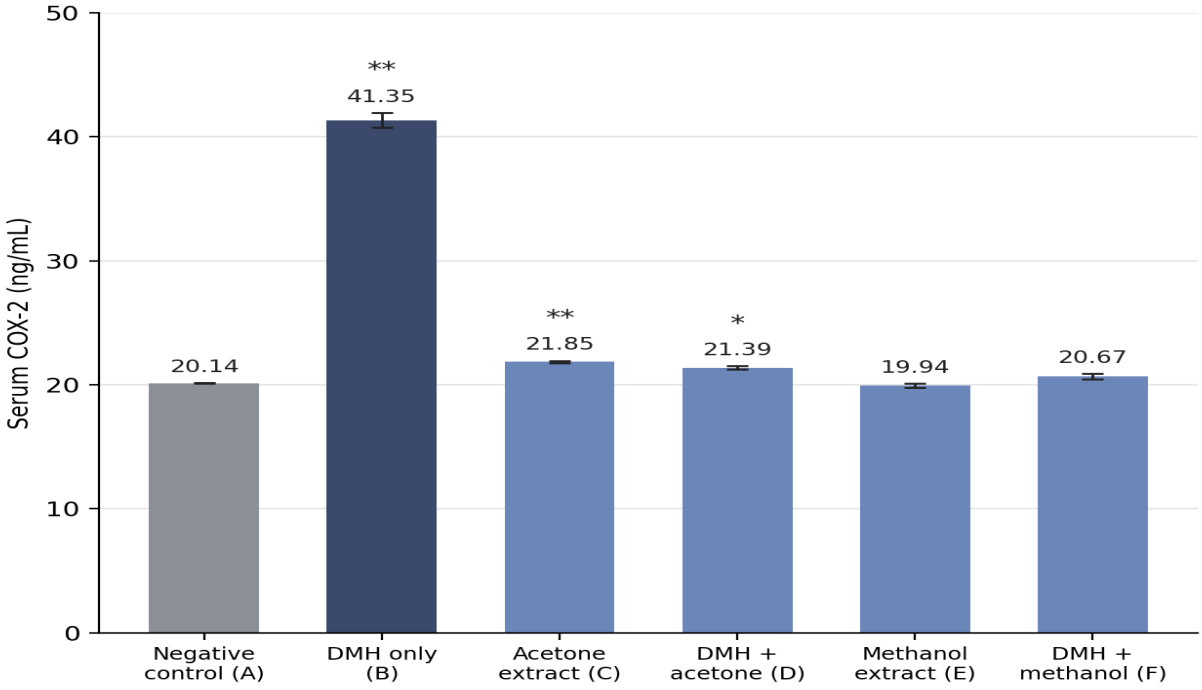


Figure 1. Effect of acetone and methanol extracts of *Zingiber officinale* on serum cyclooxygenase-2 (COX-2) concentration in N,N'-dimethylhydrazine-induced colorectal cancer rats.

Faecal Occult Blood Test

Faecal occult blood tests were positive in all DMH-induced groups (Groups B, D and F) at week 15 of DMH administration and negative in the negative control group (Group A) as well as Groups (C and E).

Macroscopic and Histopathological Findings

The macroscopic and histopathological findings are shown in Figures 2–4. At necropsy, DMH-induced groups showed inflammation of the colon and rectum, a focal necrotic lesion in a dilated caecum, enlargement of the mesenteric lymph nodes and distension of the small intestine and caecum (Figure 2). Methylene blue staining revealed aberrant crypt foci (ACF) in the colonic mucosa of DMH-induced

groups (Figure 3B), and H&E-stained sections showed focal mild-to-moderate epithelial dysplasia (Figure 3A). H&E-stained colonic sections from DMH-induced groups also showed inflammatory infiltration concentrated in the mucosa, with disruption of the crypt architecture and epithelial erosion (Figure 4A, C). In contrast, the colon of the control rat retained its normal crypt architecture, with only a mild inflammatory infiltrate (Figure 4B).

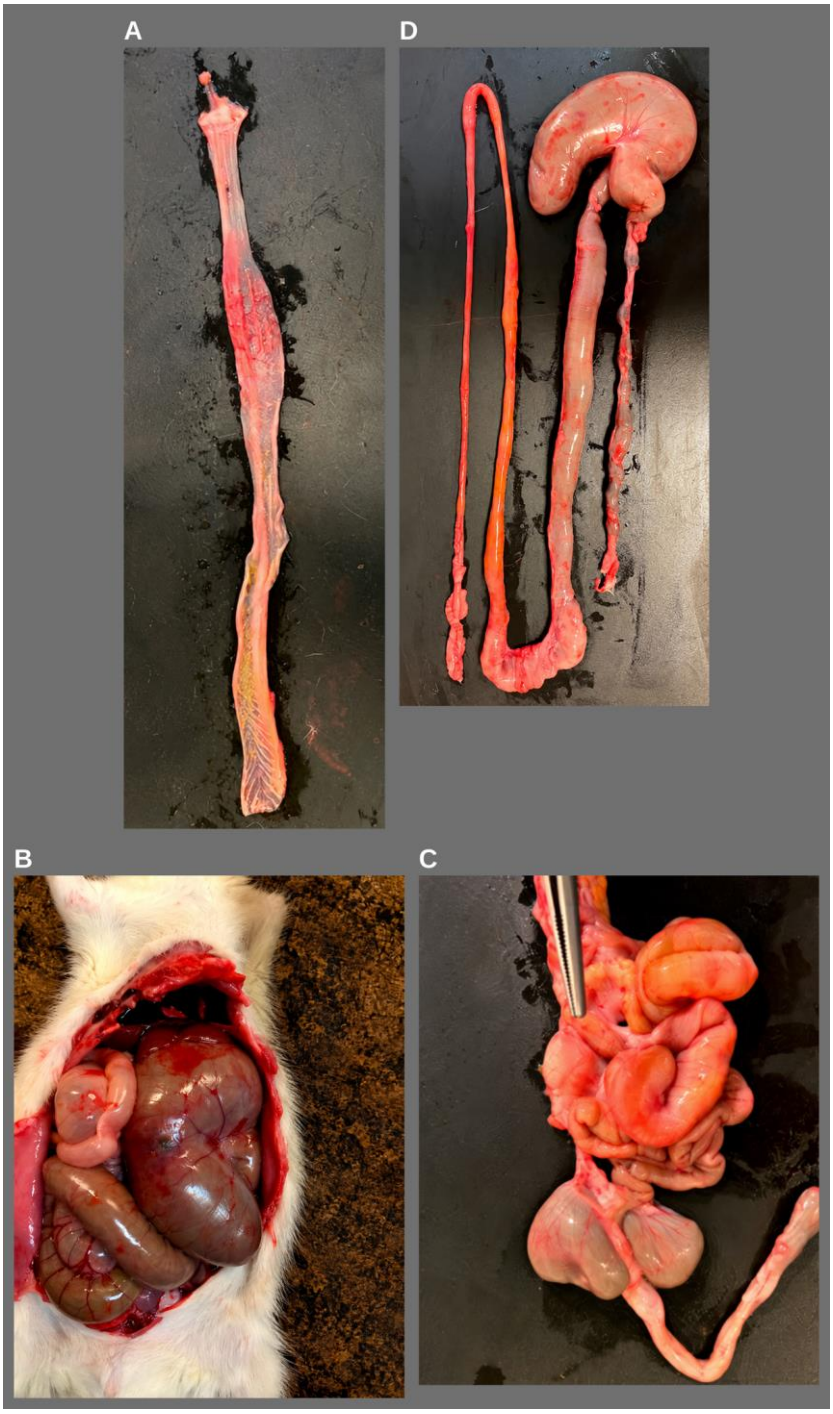


Figure 2. Macroscopic appearance of the small and large intestines of DMH-induced groups. (A) Inflammation of the colon and rectum. (B) Focal necrotic lesion in a dilated caecum. (C) Enlarged mesenteric lymph nodes. (D) Distension of the small intestine and caecum.

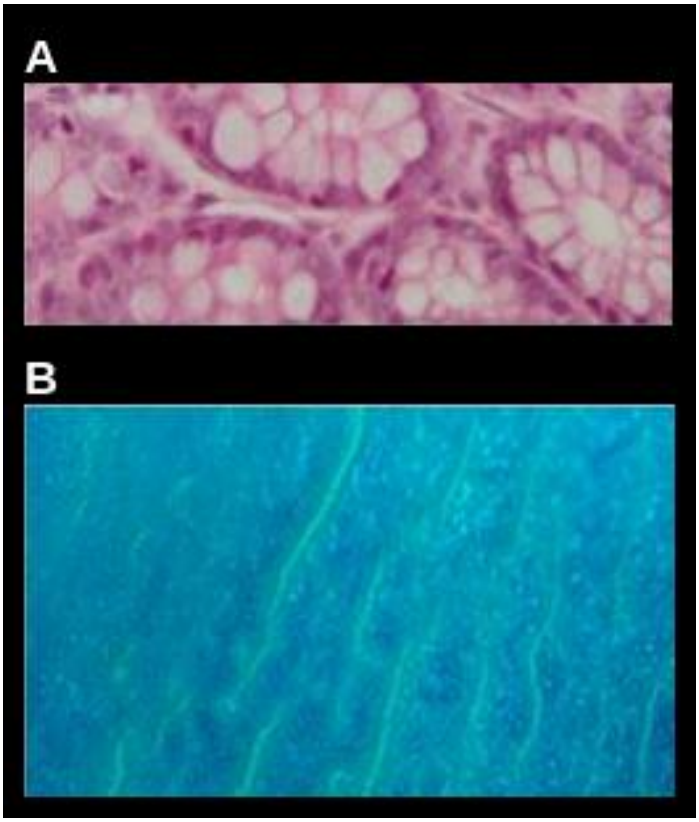


Figure 3. Preneoplastic colonic lesions in DMH-induced groups. (A) Focal mild-to-moderate epithelial dysplasia (H&E staining). (B) Aberrant crypt foci in the colonic mucosa (methylene blue staining, stereomicroscope).

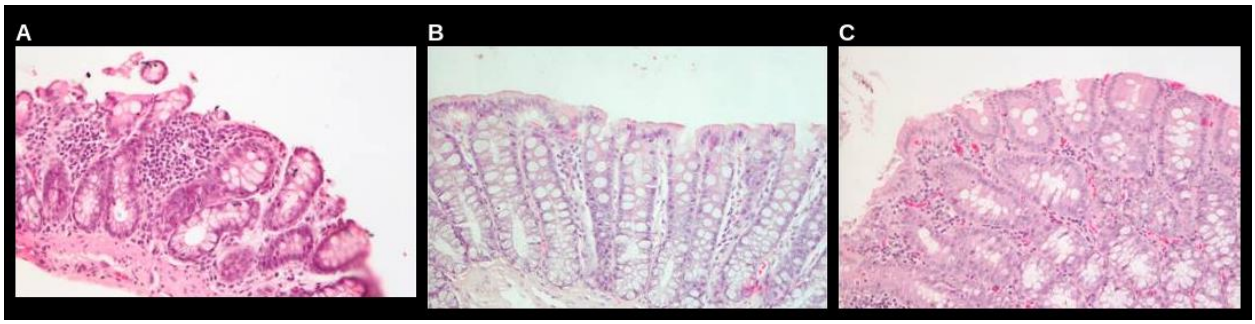


Figure 4. Histopathological evaluation of colonic inflammation (H&E staining). (A, C) Colon of DMH-induced groups showing inflammatory infiltration predominantly in the mucosa, disruption of the crypt architecture and epithelial erosion. (B) Colon of a control rat showing preserved crypt architecture with only a mild inflammatory infiltrate.

Antioxidant Capacity of Ginger Extracts

The antioxidant capacities of the acetone and methanol extracts of *Zingiber officinale* and the ground ginger reference sample, as measured by the Trolox Equivalent Antioxidant Capacity (TEAC) and Oxygen Radical Absorbance Capacity (ORAC) assays, are presented in Table 4 and Figure 5. The methanol extract exhibited the highest TEAC and ORAC values, followed by the acetone extract, while the ground ginger reference sample recorded the lowest antioxidant capacity. Both extracts showed significantly higher antioxidant capacities than the ground ginger reference ($p \leq 0.01$).

Table 4: Antioxidant capacity of ginger extracts (TEAC and ORAC)

Extract/Sample	*TEAC (µmol Trolox eq/100 g)*	*ORAC (µmol Trolox eq/100 g)*
Acetonic Extract	*67.85 ± 0.02 ***	*72,075.50 ± 3.23 ***
Methanolic Extract	*73.02 ± 0.01 ***	*81,229.50 ± 1.94 ***
Ground Ginger (Reference)	*44.79 ± 0.01*	*41,265.00 ± 1.15*

*Mean ± SEM. **p ≤ 0.01 vs ground ginger.*

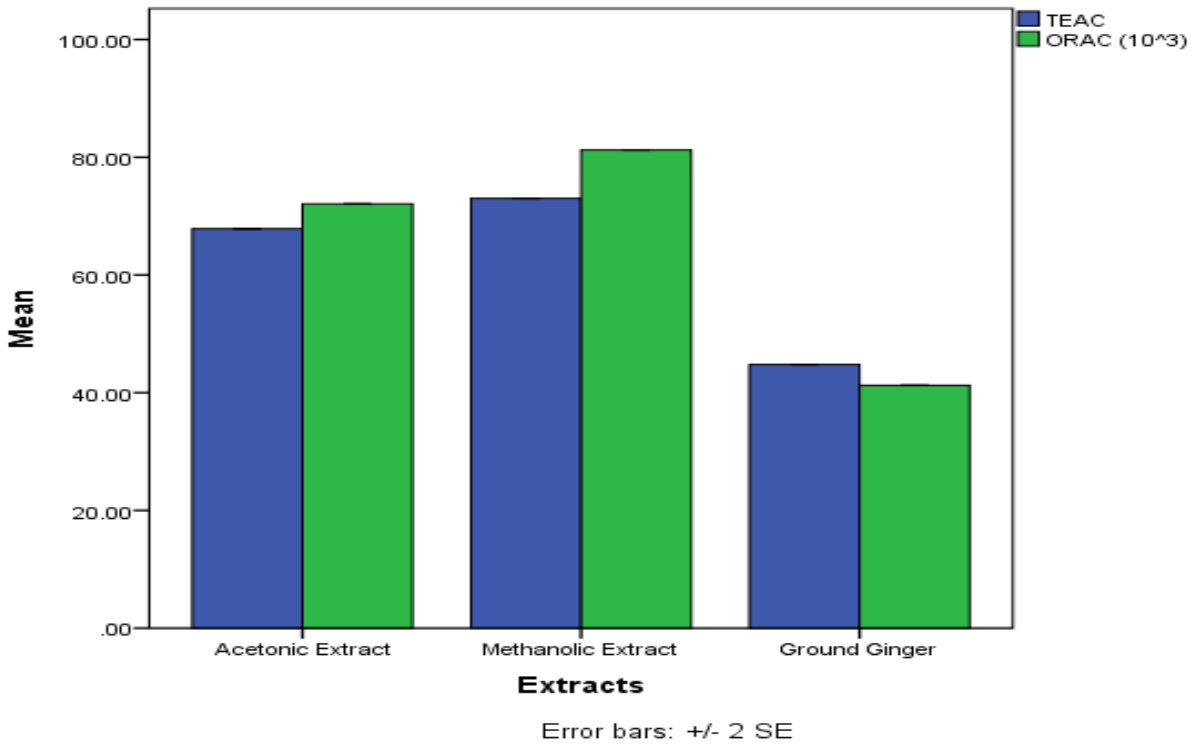


Figure 5. Antioxidant capacity of acetone and methanol extracts of *Zingiber officinale* compared with ground ginger (reference), TEAC and ORAC in µmol Trolox equivalents/100 g (ORAC plotted ×10³). Error bars represent ± 2 SE.

DISCUSSION

In this study, we compared acetone and methanol extracts of *Zingiber officinale* rhizome for anti-inflammatory and antioxidant activity in N,N'-dimethylhydrazine (DMH)-treated Wistar rats. DMH administration approximately doubled serum cyclooxygenase-2 (COX-2) concentration and was accompanied by positive faecal occult blood tests, whereas treatment with either extract returned COX-2 towards the values of untreated controls. The methanol extract was the more effective of the two: COX-2 in DMH-induced groups receiving the methanol extract did not differ significantly from the negative control, whereas values in the acetone-treated DMH group remained modestly but significantly elevated. The methanol extract also showed the highest Trolox Equivalent Antioxidant Capacity (TEAC) and Oxygen Radical Absorbance Capacity (ORAC). Together, these findings indicate that ginger rhizome extracts can attenuate DMH-associated inflammation, with the more polar methanol extract showing the stronger anti-inflammatory and antioxidant profile.

The two-fold rise in serum COX-2 in the DMH-only group is consistent with the established link between chronic inflammation and colorectal carcinogenesis. DMH is metabolised in the liver to methylazoxymethanol, which reaches the colon and generates the methyldiazonium ion, an alkylating agent that causes DNA damage, oxidative stress and inflammatory infiltration of the colonic mucosa [29]. In Wistar rats, DMH exposure increases colonic oxidative stress and inflammatory mediators, including COX-2 [36], and COX-2 is overexpressed in a large proportion of human colorectal adenomas and carcinomas [9], where its principal product, prostaglandin E2 (PGE2), promotes proliferation, angiogenesis and resistance to apoptosis [11]. The

positive faecal occult blood tests in the DMH-induced groups further support the presence of DMH-induced mucosal injury, although this test alone does not establish neoplasia.Because these tests were positive at week 15, before the extracts were given, they indicate that mucosal injury was already established when treatment began.

Macroscopic and histopathological examination provided morphological confirmation of DMH-induced colonic injury and early neoplastic change. Aberrant crypt foci (ACF) were identified in the colonic mucosa of DMH-induced groups. ACF are the earliest lesions of colorectal carcinogenesis that can be recognised microscopically and are widely used as intermediate biomarkers in DMH- and azoxymethane-induced models [29]; their presence here agrees with previous reports of ACF formation in rats exposed to DMH [37,38]. Focal mild-to-moderate epithelial dysplasia was also observed. ACF are histologically heterogeneous, ranging from hyperplastic, non-dysplastic crypts to dysplastic foci, and it is the dysplastic subset that is regarded as truly preneoplastic and more likely to carry genetic alterations [29]. The coexistence of ACF and dysplasia therefore indicates that the DMH regimen used here initiated colorectal carcinogenesis, complementing the biochemical evidence provided by serum COX-2 and the faecal occult blood test. Abdel-Rasol et al. similarly reported DMH-induced histopathological alterations in the rat colon that were attenuated by ginger extract administered over 21 weeks [31].

DMH-associated injury was not confined to the colon. Gross examination revealed distension of the small intestine and caecum, a focal necrotic lesion in the caecum and enlarged mesenteric lymph nodes, while H&E-stained colonic sections from DMH-induced groups showed mucosal inflammatory infiltration with architectural disruption and epithelial erosion. Enteric microorganisms may contribute to such inflammation in experimental models [39], and intestinal inflammation can in turn alter the microbiota and enhance its genotoxic, cancer-promoting activity [40]. Chronic inflammation is an established risk factor for colorectal cancer: infiltrating inflammatory cells release mediators such as interleukin-6 and reactive oxygen species that can amplify DNA damage in the epithelium, and the progression from inflammation to neoplasia appears to depend substantially on COX-2 and nuclear factor-κB (NF-κB) signalling [41]. The mucosal inflammation observed histologically is thus in keeping with the elevated serum COX-2 in the DMH-only group.

Both extracts reduced serum COX-2 in DMH-induced groups by approximately half relative to the DMH-only group. This agrees with the findings of Manju and Nalini, in whose study oral ginger lowered tumour incidence and lipid peroxidation whether given during or after DMH initiation [19]. Mechanistically, [6]-gingerol prevents COX-2 induction by inhibiting activation of p38 MAPK and NF-κB [42], and a standardised ginger extract has been shown to attenuate carcinogen-induced inflammation and oxidative stress in vivo [43]. Clinical data point the same way: ginger root extract decreased mucosal COX-1 in people at elevated CRC risk [20] and lowered colonic eicosanoids in average-risk volunteers [21]. The present study extends this evidence by directly comparing two solvent extracts, showing that the methanol extract restored serum COX-2 to control levels, whereas the acetone extract produced a slightly smaller effect. Because the extracts were administered only after DMH induction had been completed, the present design assesses the effect of ginger on established DMH-induced inflammation rather than on the initiation of carcinogenesis.

Potential Phytochemical Basis of the Anti-inflammatory Activity of Ginger

The significant reduction in serum concentrations of cyclooxygenase-2 (COX-2) following administration of both acetone and methanolic extracts of ginger may be linked to certain constituents of *Zingiber officinale*, particularly gingerols, shogaols and paradols. These compounds are plausible contributors because studies that combined chemical characterization with biological analysis have shown activity against inflammation-related endpoints. For instance, Jolad et al., using mass spectrometry and chromatographic methods, established that fractions containing gingerols and their derivatives prevented lipopolysaccharide-induced prostaglandin E_2 (PGE_2) production [44]. However, the presence and concentrations of these compounds could not be confirmed because phytochemical profiling was not performed in this study.

Modulation of the cyclooxygenase pathway is one plausible mechanism. Van Breemen et al. identified COX-2-binding compounds in a fraction of a methanolic ginger extract and showed that purified 10-gingerol, 8-shogaol and 10-shogaol inhibited COX-2 [45]. Furthermore, Tjendraputra et al. showed that 8-paradol and 8-shogaol inhibited COX-2 activity in intact cells [46]. These components may contribute to altered inflammatory mediator

production if they were present in the extracts under investigation at biologically effective quantities. However, inhibition of enzyme activity does not necessarily lower the serum concentration of COX-2 protein.

A second possibility involves effects on COX-2 expression. Using high-performance liquid chromatography to characterise gingerol-rich and shogaol-rich preparations, Lantz et al. showed that both prevented PGE_2 production in stimulated U937 cells; under the same conditions, gingerol-containing preparations also inhibited COX-2 expression, whereas shogaol-containing extracts did not [47]. These results imply that different ginger constituents act at different stages of inflammatory signalling. Direct examination of COX-2 expression and downstream mediators would therefore be necessary to establish any correlation between extract composition and the present serum findings.

Other inflammatory mechanisms may also be involved. Sang et al. isolated and characterised ginger compounds and found that 6-shogaol inhibited arachidonic acid release and nitric oxide synthesis in activated macrophages more effectively than 6-gingerol [48]. This was corroborated by Dugasani et al., who found that gingerols and 6-shogaol inhibited the production of PGE_2 and nitric oxide, with 6-shogaol showing the highest activity [49]. These findings are consistent with the possibility that several constituents contribute through complementary mechanisms; however, additive or synergistic effects were not examined in the present study.

Furthermore, Ezzat et al. combined phytochemical isolation with anti-inflammatory testing, identifying 6-shogaol and 1-dehydro-6-gingerol among the active isolates, and observed that an aqueous ginger extract reduced inflammatory responses in a rat paw-oedema model; however, these in vivo findings were obtained with the whole extract and cannot attribute the effect to individual compounds [50]. Together, these studies provide a rationale for investigating ginger phytochemicals as probable contributors to the present findings. Confirming this would require chromatographic characterization of the experimental extracts, quantitative measurement of the active compounds and functional analysis of tissue inflammatory endpoints.

Both extracts showed substantially higher antioxidant capacity than ground ginger, with the methanol extract giving the highest TEAC and ORAC values. The phenolic constituents of ginger, chiefly gingerols and shogaols, are effective radical scavengers and limit lipid peroxidation [51,52]. The superior performance of methanol is consistent with the general observation that polar and semi-polar solvents recover more phenolic antioxidants from plant material than less polar solvents [53], and with the higher extraction yield obtained with methanol in this study (12.7% vs 9.8%). Because oxidative stress promotes NF-κB activation and consequent COX-2 induction [36,42], the greater antioxidant capacity of the methanol extract may partly explain its stronger effect on serum COX-2. However, TEAC and ORAC were measured on the extracts in vitro rather than in the animals' serum, so this link remains inferential.

An unexpected finding was that healthy rats given the acetone extract alone (Group C) had significantly higher serum COX-2 than the negative control (21.85 ± 0.09 vs 20.14 ± 0.01 ng/mL; $p < 0.001$), whereas the methanol extract alone (Group E) did not alter COX-2 ($p = 0.99$). The increase was small (approximately 8%) compared with the doubling produced by DMH, and its biological relevance is uncertain. Possible explanations include differences in the spectrum of constituents recovered by solvents of different polarity [53], effects of the vehicle used to suspend the less water-soluble acetone extract, or traces of residual solvent. Ginger given by gavage at doses well above 300 mg/kg has been reported to be well tolerated in rats [33], but the present observation indicates that the acetone extract should not be assumed to be inert in healthy animals and warrants dose–response and toxicological evaluation. By contrast, the absence of any effect of the methanol extract on basal COX-2 in healthy rats supports its suitability for further investigation as a natural anti-inflammatory agent.

Limitation

Formal botanical authentication and voucher specimen deposition were not performed at the time of the study; therefore, a voucher specimen number could not be provided. The acetone and methanol extracts were not subjected to phytochemical characterization, precluding identification and quantification of the specific bioactive constituents responsible for the observed effects. Future studies should incorporate formal botanical authentication with voucher specimen deposition, comprehensive phytochemical profiling. In addition, COX-2 was measured in serum rather than in colonic tissue, so serum concentrations may not fully reflect mucosal COX-2 expression, and tumour incidence and multiplicity were not quantified. Furthermore, histopathological assessment was descriptive and limited to selected groups; ACF were not

enumerated and lesions were not graded, so the effect of the extracts on structural colonic lesions could not be quantified.

CONCLUSION

In this study, both acetone and methanol extracts of ginger rhizome significantly lowered serum COX-2 relative to untreated DMH-exposed rats, indicating anti-inflammatory activity in this model. A superior antioxidant capacity was demonstrated by the methanolic extract. Macroscopic and histological findings, including aberrant crypt foci and focal epithelial dysplasia, confirmed that DMH induced preneoplastic colonic lesions in this model. These findings support *Zingiber officinale* as a potential supportive agent against DMH-induced inflammation that targets the COX-2 inflammatory axis. Future research should include testing how individual ginger constituents affect RAS pathway activation, profiling gene expression, and examining clinical relevance in *KRAS*- and *NRAS*-stratified patient cohorts.

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AUTHORS' CONTRIBUTION

MSKA: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **AJF:** Conceptualization, Methodology, Investigation, Writing – original draft. **ABJ:** Conceptualization, Methodology, Investigation, Writing – original draft. **SOA:** Conceptualization, Methodology, Investigation Writing – review & editing. **BES:** Conceptualization, Methodology, Investigation Writing – review & editing. MB**:** Conceptualization, Methodology, Investigation, Writing – review & editing. **ABA:** Methodology, Investigation, Writing – original draft. **BO:** Methodology, Investigation, Writing – review & editing. **FA:** Supervision, Conceptualization, Methodology, Resources, Project administration. All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest. This study was conducted as an undergraduate research project at Ladoke Akintola University of Technology, Osogbo, Nigeria, in 2019, with no external funding received.

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