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The Journal of Phytopharmacology 2026; 15(1):94-98
Online at: www.phytopharmajournal.com

The Journal of Phytopharmacology
(Pharmacognosy and phytomedicine Research)

Research Article

ISSN 2320-480X
JPHYTO 2026; 15(1): 94-98
January- February
Received: 07-01-2026
Accepted: 25-03-2026
Published: 30-03-2026
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doi: 10.31254/phyto.2026.15113

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Evaluation of anticancer activity of *Malus domestica* in DMBA-induced breast cancer in rats

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ABSTRACT

Background: Breast cancer remains one of the most prevalent malignancies worldwide, with oxidative stress and inflammatory mediators such as TNF-α playing a critical role in tumor progression. Natural products, including *Malus domestica* (apple), are rich in polyphenols and antioxidants that have shown potential anticancer effects. Therefore, exploring plant-based interventions may provide safer and effective adjunct therapies for the management of breast cancer. The present study has been designed to evaluate the tumor regression properties of apple in a rat model with DMBA-induced mammary tumors. **Objective:** To evaluate the anticancer activity of *M. domestica* extract in DMBA-induced breast cancer in rats by assessing tumor regression, oxidative stress markers (LPO), inflammatory marker (TNF-α), hormonal levels, and histopathological changes. **Materials and Methods:** Female Charles Foster rats were used for the study and mammary tumors were induced by oral administration of 7,12-dimethylbenz[a]anthracene (DMBA) (20 mg/mL) dissolved in olive oil. After tumor development, rats were treated orally with Malus domestica (apple) extract (2 mg/kg body weight) for four weeks. Tumor size was measured to assess regression. Biochemical parameters including lipid peroxidation (LPO), TNF-α, estradiol, and progesterone levels were analyzed. Histopathological examination of mammary tissue was also performed to evaluate cellular changes and therapeutic response. **Results:** Treatment with *M. domestica* extract for four weeks resulted in a marked reduction in tumor size (from 1.8 cm to 0.8 cm). A significant decrease (***$p < 0.0001$) in lipid peroxidation (LPO) and serum TNF-α levels (****$p < 0.0001$) was observed compared to the DMBA-treated group. Estradiol levels were reduced, while progesterone levels showed no significant change. Histopathological analysis revealed increased apoptosis, reduced mitotic activity, and decreased inflammatory cell infiltration, indicating a positive anticancer effect of the treatment. **Conclusion:** *M. domestica* extract exhibits significant anticancer activity in DMBA-induced breast cancer in rats by reducing tumor size, oxidative stress, and inflammatory markers. These findings suggest that apple may serve as a potential adjuvant therapy in the management of breast cancer.

Keywords: *Malus domestica*, Breast Cancer, DMBA, Tumor Regression, Oxidative Stress, Apoptosis.

INTRODUCTION

The significance of nutritional supply in tumor formation and treatment response is increasingly recognized due to a growing understanding of cancer metabolism. Cancers exhibit diverse metabolic requirements determined by genetics, the microenvironment, and the tissue of origin. Therefore, dietary modifications need to be tailored to the specific characteristics of both the cancer and its therapy. Extensive research has shown that secondary plant metabolites, known as phytochemicals and commonly found in fruits, possess oncopreventive and chemoprotective effects. Apples are widely consumed fruits available year-round and are a rich source of phytochemicals. As one of the best sources of antioxidant phenolic compounds in the Western world, apples are an important component of the diet [1].

Apple extracts have been demonstrated to have powerful antioxidant activity and antiproliferative activity against breast, liver, and colon cancer cells *in vitro* in a dose-dependent manner [2-5]. Within the group of 21 fruits and vegetables that are typically consumed in the United States, apples were ranked second for total phenolic content and had the second greatest total antioxidant activity [3-6].

Researchers Rui *et al*. 2005 [7] found that apple extracts prevented the development of mammary cancer in rats that had been caused by 7,12-dimethylbenz(a)anthracene (DMBA) in a dose-dependent way. Mammary tumours in rodents can be caused by the chemical carcinogen known as DMBA, which is commonly used in practice. The disruption of tissue redox balance that occurs throughout the process of DMBA-induced carcinogenesis is what ultimately results in oxidative stress, which in turn causes biochemical and pathophysiological abnormalities in rats [4-5]. Through the process of lipid peroxidation, the production of reactive oxygen species is responsible for the initiation of cellular injury, which in turn causes changes at both the cellular and subcellular levels. It has been noticed that the incidence of cancers that are oestrogen receptor-positive has been on the rise, whereas the incidence of cancers that are oestrogen receptor-negative has been on the decline [6]. These cancers are impacted by oestrogen, which encourages the proliferation of cancer cells [8]. Oestrogen receptor-positive cancers are affected by oestrogen [9]. The compound known as 7,12-dimethylbenz(a)anthracene (DMBA) is considered to be one of the most potent carcinogens that can cause cancer in the mammary glands of animals, including rodents [10].

The aim of this study is to examine the properties of apple associated with tumor regression in a DMBA-induced mammary tumor rat model.

MATERIAL AND METHODS

Chemicals and reagents

7,12-Dimethylbenz[a]anthracene (DMBA) was procured from Sigma-Aldrich, USA (Product No. D3254-1G; CAS No. 57-97-6; Lot No. SLBX1136; P Code: 1002660800) through a scientific chemical supplier in Patna, Bihar, India. All other solvents and chemicals used in the study were of analytical grade, with a purity of 99%. Estradiol (Lot No. EIA-49K2I8) and progesterone (Lot No. EIA-48K2E8) ELISA kits were obtained from Monobind Inc. (100 North Pointe Drive, Lake Forest, CA 92630, USA). A rat TNF-α ELISA kit (Cat. No. 872.010.001) was obtained from Diaclone, France.

Extraction of *M. domestica*

Red Delicious apples were purchased from the local market. Prior to extraction, the fresh apples were washed and dried. The extraction was carried out using a previously reported method [3,4]. Briefly, 100 g (fresh weight) of the edible portion of apples was weighed and homogenized with chilled 80% acetone (1:2, w/v) using a chilled Waring blender for 5 min. The homogenate was further processed for 3 min using a Polytron homogenizer. The mixture was then filtered through Whatman No. 1 filter paper using a Büchner funnel under vacuum.

The filtrate was concentrated at 45°C to less than 10% of the initial volume. The apple phytochemical extract was reconstituted with distilled water to obtain a final concentration equivalent to 2 g fresh apple per mL. The extract was freeze-dried and stored at -40 °C until use in the feeding trial. Control extracts were prepared using the same solvents and procedures without apple material.

Animals

A total of eighteen female Charles Foster rats were obtained from the animal facility of Mahavir Cancer Sansthan and Research Centre, Patna, India. All animals were maintained under standard laboratory conditions, with free access to a standard diet and drinking water. The rats were acclimatized for seven days prior to the start of the experiment and housed in standard polypropylene cages (two animals per cage). The animal facility was maintained at a temperature of 22 ± 2 °C with a 12-hour light/dark cycle. Animals were randomly assigned to control and treatment groups.

All applicable international, national, and institutional guidelines for the care and use of laboratory animals were strictly followed. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) of Mahavir Cancer Sansthan and Research Centre, Patna, India (Protocol No. 2021/1F-06/10/21). All procedures were conducted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi. The study did not involve any human participants.

Experimental design

A total of eighteen female Charles Foster rats, aged 55-60 days and weighing 150 ± 10 g, were divided into three groups of six animals each. Group I served as the control, Group II received only DMBA, and Group III received apple extract following DMBA-induced tumor development. The extract was administered orally at a dose of 2 mg/kg body weight daily for four weeks after tumor formation (approximately 0.5 cm in size).

At the end of the treatment period, rats were anesthetized and euthanized using diethyl ether during the diestrous phase of the estrous cycle. Blood samples were collected via cardiac puncture, and serum was separated for biochemical analysis, including lipid peroxidation, tumor necrosis factor-alpha (TNF-α), and hormonal assays (estrogen and progesterone). Mammary tissues were excised and preserved in 10% formalin for histopathological examination.

Tumour Model

Mammary tumors were induced in female Charles Foster rats aged 7-8 weeks and weighing 150 ± 10 g. A single freshly prepared dose of 7,12-dimethylbenz[a]anthracene (DMBA) (15 mg/mL), dissolved in maize oil, was administered intragastrically using a gavage method. A total of eight rats were used for tumor induction.

Tumor development was monitored by weekly palpation starting from the fourth week after DMBA administration. The first palpable tumors appeared at the sixteenth week, and by the eighteenth week, all animals had developed tumors [11].

Tumor size was measured using a Vernier caliper. Tumor volume (V) was calculated using the formula: $V\ (cm^3) = (L \times B^2)/2$, where L is the largest diameter and B is the smallest diameter measured perpendicular to L, both expressed in centimeters.

Lipid peroxidation assay

Thiobarbituric acid reactive substances (TBARS), which are indicative of lipid peroxidation, were estimated using the double-heating method [12]. This method is based on the spectrophotometric measurement of the color produced by the reaction between malondialdehyde (MDA) and thiobarbituric acid (TBA).

In this assay, 0.5 mL of serum was mixed with 2.5 mL of 10% trichloroacetic acid (TCA) in a centrifuge tube and heated in a water bath at 90 °C for 15 min. After cooling to room temperature, the mixture was centrifuged at 3000 rpm for 10 min. Then, 2 mL of the supernatant was mixed with 1 mL of 0.675% TBA solution in a test tube. The mixture was again heated at 90 °C for 15 min and subsequently cooled to room temperature. The absorbance was measured at 532 nm using a UV-Vis spectrophotometer (Thermo Scientific, USA; UV-10).

Hormonal analysis

Hormonal evaluation was performed using the ELISA technique. The concentrations of estradiol and progesterone were determined according to the manufacturer’s instructions.

For estradiol estimation, 25 µL of serum samples were dispensed into microplate wells following standard calibration. Then, 50 µL of estradiol biotin reagent was added to each well, mixed gently, and incubated at room temperature for 30 min. Subsequently, 50 µL of estradiol enzyme reagent was added, mixed, and incubated for 90 min at room temperature. The wells were aspirated, washed three times with wash buffer, and blotted. Next, 100 µL of substrate solution was added and incubated for 20 min. Finally, 50 µL of stop solution was added, and absorbance was measured at 450 nm (reference wavelength 620-630 nm) using a Merck ELISA reader. Results were expressed in pg/mL.

For progesterone estimation, 25 µL of serum samples were added to microplate wells along with the standard calibration range. Then, 50 µL of progesterone enzyme reagent was added, followed by gentle mixing. Subsequently, 50 µL of progesterone biotin reagent was added, mixed, and incubated at room temperature for 60 min. The wells were aspirated, washed three times with 350 µL wash buffer, and blotted. Then, 100 µL of substrate solution was added and incubated for 20 min. Finally, 50 µL of stop solution was added, and absorbance was measured at 450 nm (reference wavelength 620-630 nm) using a Merck ELISA reader. Results were expressed in ng/mL.

Detection of TNF-α

Serum levels of TNF-α were determined using the ELISA technique. A rat TNF-α ELISA kit was used according to the manufacturer's instructions. The capture antibody was pre-coated onto the microwell plate.

Briefly, 100 µL of standard diluent and 100 µL of serum samples were added to the designated wells. Then, 50 µL of diluted detection antibody was added to each well, and the plate was incubated at room temperature for 3 h. After incubation, the contents were discarded, and the wells were washed three times with 300 µL of wash buffer.

Subsequently, 100 µL of streptavidin-HRP solution was added to each well and incubated at room temperature for 30 min. The wells were again washed three times with 300 µL of wash buffer. Then, 100 µL of TMB substrate solution was added to each well and incubated for 5-15 min at room temperature in the dark. The reaction was stopped by adding 100 µL of stop solution to each well. Absorbance was measured at 450 nm (reference wavelength 620-630 nm) using a Merck ELISA reader, and results were expressed in pg/mL.

Histopathology

Breast tissue specimens were fixed in 10% formalin for 24 h. The tissues were then dehydrated using ethanol, embedded in paraffin, and sectioned into 5 µm thick slices. The sections were stained with hematoxylin and eosin (H&E) and examined under a light microscope for histological evaluation.

Statistical analysis

Results are presented as mean ± standard error of the mean (SEM). Differences in tumor volume between DMBA-treated and treatment groups were analyzed using two-way analysis of variance (ANOVA), with time and treatment regimen as independent variables. For all other parameters, statistical significance between control and treatment groups was determined using one-way ANOVA followed by Tukey's post hoc test for multiple comparisons. A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism 5 software (GraphPad Software Inc., San Diego, USA).

RESULTS

In the present investigation, the anticancer property of whole (skin & pulp) apple extract was evaluated on a DMBA-induced breast tumor model on Charles Foster rats. A 2 mg/ml dose of extract was administered to a DMBA-induced breast tumor model on rats, and the efficacy of apple was observed through tumor volume, lipid peroxidation (LPO) test, estradiol and progesterone levels, serum TNF-α level, and histopathological examination of mammary tissue. The following findings were observed after administration of apple extract for 4 weeks i.e. reduction in tumor size was observed from 1.2 cm to 0.6 cm (Figure 1). Reduction in tuomor size with significant decrease in LPO level which is marked by MDA levels was also observed (Figure 2). Decrease in level of estradiol was observed as compared to DMBA treated (Figure 3), however no changes in serum progesterone level were observed (Figure 4). The decreased serum TNF-α level was also observed (Figure 5) as compared to DMBA treated. On the other hand, histopathological study showed in control rat showing mammary tissue section of normal arrangement of adipocytes, and lobules (Figure 6A), The presence of pleomorphism, high mitotic activity, necrosis and stromal invasion confirm the malignant nature of the lesion induced by DMBA (Figure 6B), Evidence of apoptosis and necrosis and Inflammatory and stromal response suggests that apple may exert anticancer effects via apoptosis induction, immune activation, and inhibition of proliferation (Figure 6C).

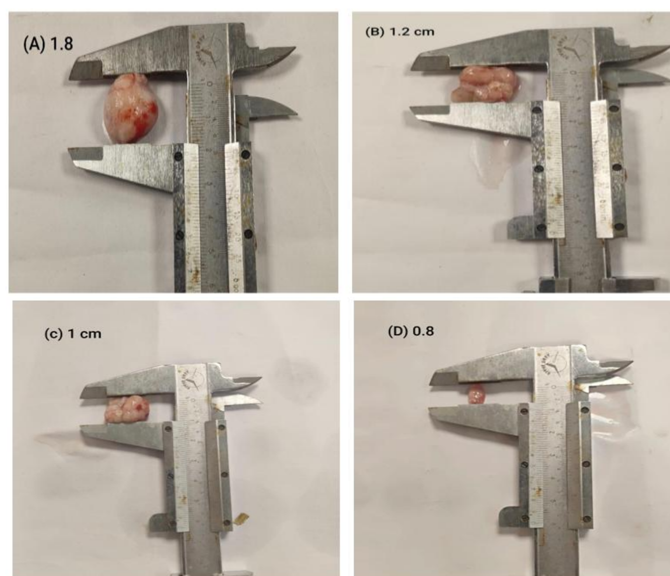

Figure 1: Effect of apple extract treatment on tumor size reduction in duration of 4 weeks. DMBA treated tumor (A) and (B, C, D) showing effect of apple extract treatment

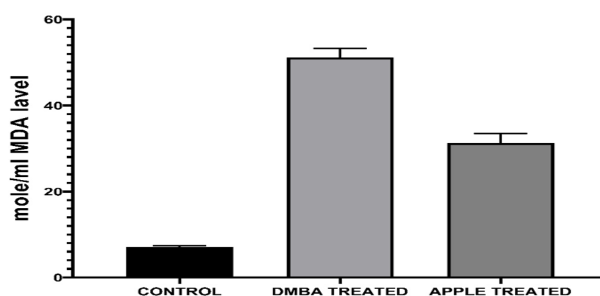

Figure 2: Effect of different treatment on lipid peroxidation level in the studied groups (n=6, significant ***p<0.0001compared with DMBA treated group, values are expressed as mean±SEM)

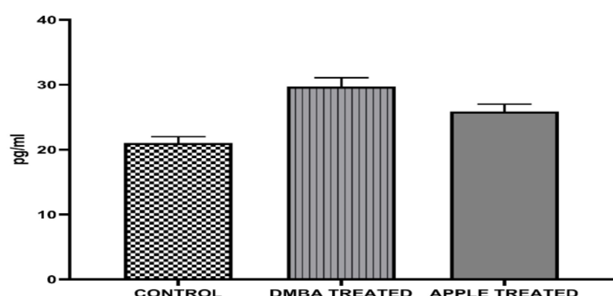

Figure 3: Effect of treatments on estradiol level in the studied groups (n=6, p<0.05, values are expressed as mean±SEM)

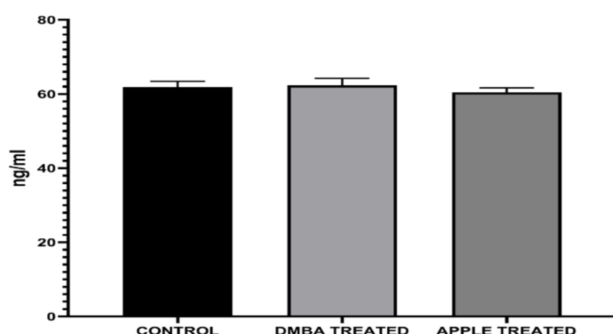

Figure 4: Effect of different treatments on progesterone level in the studied groups (n=6, p>0.05(NS), values are expressed as mean±SEM)

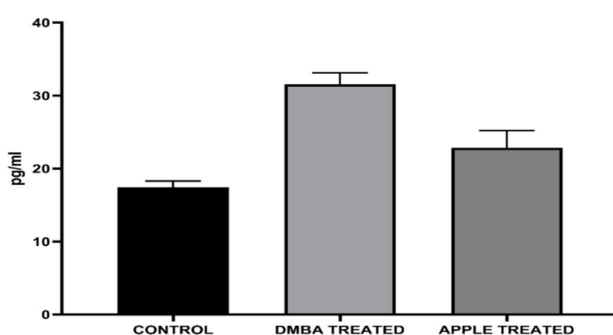

Figure 5: Effect of different treatments on serum TNF-α level in the studied groups (n=6, ****p<0.0001 compared with control group, **p< 0.0001 compared with olive oil treated group, values are expressed as mean±SEM)

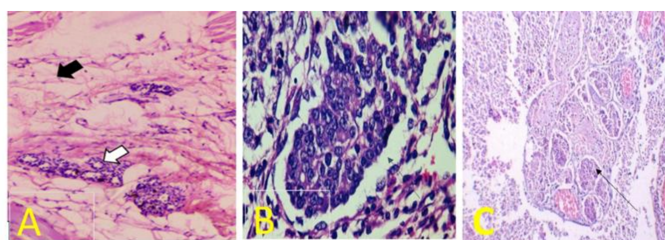

Figure 6: A control rat showing mammary tissue section of normal arrangement of adipocytes (black arrow), and lobules (white bold arrow) at X500 (A). The image (H&E, 40x) shows high-grade mammary adenocarcinoma induced by DMBA. The presence of pleomorphism, high mitotic activity, necrosis and stromal invasion confirm the malignant nature of the lesion. Focal coagulative necrosis is present, particularly in central tumour areas, likely due to rapid proliferation outpacing blood supply. Apoptotic bodies are seen at the periphery of tumour lobules. (B). The image (H&E, 10x) shows a mixture of solid and glandular patterns, indicating moderately differentiated adenocarcinoma. Tumour cells exhibit moderate pleomorphism, with oval to irregular hyperchromatic nuclei. The tumour exhibits feature of moderate regression under apple treatment like Reduced mitotic activity, Evidence of apoptosis and necrosis and Inflammatory and stromal response. It Suggests that apple may exert anticancer effects via apoptosis induction, immune activation, and inhibition of proliferation

DISCUSSION

In the present investigation after administration of apple extract for 4 weeks reduction in tumor size was observed from 1.8 cm to 0.8 cm which is a significant reduction. Reduction in tuomor size was associated with a significant decrease in LPO level which is marked by MDA levels. The decrease in MDA levels exhibit the inhibitor activity of apple extract in production of LPO levels. It means apple helps to reduce oxidative stress in the rats. Apple phytochemicals are suggested to have many chemo-preventive and chemo-protective effects against various types of cancer. These effects include regulation of proliferation, cell cycle, apoptosis, reactive oxygen species (ROS), and anti-inflammatory activities [13-17] which supports the present study.

The decreased serum TNF-α level was also observed in my study which shows anti-inflammatory and anti-proliferative property of apple. Apples contain a wide variety of phytochemicals, including triterpenoids, organic acids, fatty acids, and apple phenolic compounds that could be reason to observe reduction in tumor volume, LPO levels and TNF-α levels were observed as compared to DMBA treated in the present study. Apple consumption specifically was associated with lower cancer incidence in several observational studies. Apple consumption was associated with decreased breast cancer incidence in a fruit and vegetable study conducted on pooled cohorts [18] and a case-control study from Mexico in pre-menopausal women [19] which shows a fair level of agreement with study.

On the other hand, therapeutic response of apple was also observed in our present histopathological study. Apoptosis, reduced mitoses and inflammatory infiltration may reflect the anticancer potential of apple. The tumour architecture is still preserved but there is visible tumour regression in some foci a promising sign of therapeutic effect. Similar studies have also showed that consumption of apples was associated with reduced incidence of colorectal [20], oral cavity and pharynx [14,21], esophagus [14], larynx [14], ovary [14], renal [22,23], and prostate [14, 24] cancers which support the present study.

The breast cancer progression depends on various factors and important among them are steroid hormones-estrogen and progesterone that binds to the receptors present on the mammary epithelial cells leading to the growth of neoplastic cells [25,26]. In our present study a decrease in level of estradiol was observed as compared to DMBA treated, however no changes in serum progesterone level were observed. One case-control study looking at fruit and vegetable consumption in pre-menopausal women in Shanghai showed an inverse association with fruit intake and breast cancer [27] which agrees with my present work. While the study found the strongest association was with citrus fruit, consumption of 57 g/day of apple or more was also reported to reduce incidence of breast cancer in the study [27]. In a meta-analysis of 20 case-control studies and 21 cohort studies, it was shown that apple consumption was associated with a reduced risk of lung, colorectal, oral cavity, and breast cancers [28]. The above-mentioned studies are in support of my work that apple contains anticancer property due to their phenolic compounds such as phloretin, quercetin and its glycosides, chlorogenic acid, catechin, and epicatechin.

CONCLUSION

Considering all evaluated parameters related to tumor regression, it can be concluded that the whole (skin and pulp) extract of apple exhibits antiproliferative activity by slowing the progression of breast tumors in rats. Apple skin, being rich in phenolic compounds, significantly contributes to its health benefits. Therefore, consumption of whole apples with the skin, as well as different apple cultivars, may enhance potential anticancer effects.

Acknowledgements

The authors are thankful to Cytopathologists, Mahavir Cancer Sansthan & Research Centre, Patna for this valuable inputs and support.

Conflict of interest

The authors declared no conflict of interest.

Financial support

This study was supported by the Mahavir Cancer Institute, Patna.

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HOW TO CITE THIS ARTICLE
Yasmin F, Deen SPY, Kareem S, Maiti TK, Niraj PK, Ali M. Evaluation of anticancer activity of *Malus domestica* in DMBA-induced breast cancer in rats. J Phytopharmacol 2026; 15(1):94-98. doi: 10.31254/phyto.2026.15113

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