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Anti-tumour Effect of *Mangifera indica* Against DMBA Induced Breast Cancer in Rats

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Abstract

In recent times breast cancer incidences have increased manifold globally. It is the most common form of cancer worldwide. It is also the major cause of death in female cancer patients around the world. Despite various drug discoveries and advancements in medical treatment, it remains associated with a high mortality rate. *Mangifera indica* (L.) has been extensively used in the Indian medicine system Ayurveda, due to its various medicinal properties. It is the most common tree found in the Indian subcontinent and has had religious as well as social connections in life for centuries of years. However, there are very limited reports regarding its anticancer activity. Thus, the present study has been aimed to study the anticancer activity of *Mangifera indica* leaf extract on 7, 12-dimethylbenz(a)anthracene (DMBA) induced breast cancer in rats. Female Charles Foster rats, 55 – 60 days old weighing around (150±10 g) were used for the study and were induced DMBA (20 mg/mL dissolved in Olive oil) orally. After the development of breast tumors (about 0.8 cm), the rats were treated with *Mangifera indica* hydroxy-ethanolic leaf extract (200 mg/kg b.w./day) orally for 5 weeks and then the volume of the tumor was measured. *Mangifera indica* treatment showed significantly reduced mammary tumor volume ($p< 0.05$), along with significant reduction ($p< 0.0001$) in the different serum biomarkers such as TNF- α level and serum malondialdehyde (MDA) levels. Significant ($p< 0.0001$) improvement in both, the kidney and liver serum biomarker parameters were observed after the treatment with *Mangifera indica* hydroxy-ethanolic leaf extract. From the entire study, taking everything into account it can be interpreted that *Mangifera indica* hydroxy-ethanolic leaf extract possesses anti-proliferative activity by suppressing the progression of breast tumors in the rat model. The plant extract also possesses a hepato-renal protective effect. Hence, it can be targeted as a novel and safe anti-cancer drug against breast cancer.

Keywords: DMBA-induced breast model; Tumor volume; TNF alpha; *Mangifera indica*; novel drug discovery.

Introduction

In terms of mortality rates, cancer ranks second worldwide. Cancer is responsible for around one in six deaths worldwide. Breast cancer has the highest mortality rate of any female malignancy. Breast cancer accounts for about 11.7% (2,261,419) of all new cancer cases diagnosed among women in 2020 and 6.9% (684,996) of all cancer-related deaths among women in 2020 worldwide; in 2018, that figure is expected to grow to 2.1 million.

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Breast cancer accounts for 14% of all new cancer cases in India (1,62,468 cases), according to the latest data from the Global Cancer Report [1-4]. Hereditary and reproductive factors, prolonged exposure to estrogen, not nursing, and other lifestyle variables all have a role in the development of breast cancer. In addition to these, environmental variables are also thought to have a role in the onset of breast cancer. The increase in various illnesses, including breast cancer, may be traced back to improper dietary consumption and poor food quality. Today's farmers increasingly rely on pesticides as a means of increasing agricultural yields. However, xenoestrogens are present in these pesticides and are also present in food preservatives. Increased breast cancer risk is attributable to the interference of these synthetic xenoestrogens with the endocrine system. Polycyclic aromatic hydrocarbons (PAHs) found in grilled, barbecued, and smoked meat are also linked to an increased risk of breast cancer. The PAHs are pro-carcinogens that become active carcinogens after undergoing a sequence of events catalyzed by cytochrome p450 enzymes in the body [5-9]. Women are at increased risk of acquiring breast cancer due to these risk factors and their ever-changing lifestyles. Improvements in cancer treatment methods including chemotherapy, radiation, and the creation of various novel anticancer medications have been made possible by the rapid progress of modern medicine. Although these treatments are quite effective in extending cancer patients' lives, they are not without their share of drawbacks. The liver and kidneys are particularly vulnerable to the toxic effects of chemotherapy medicines. As a result, there is a pressing need for the discovery and development of cheaper, more effective, and less harmful cancer treatments. Experimental animal models show that medicinal herbs and dietary supplements may be extremely successful as chemo-preventive and anticancer medicines with acceptable safety profiles [10]. The South and Southeast Asian fruit *Mangifera indica* L. is from the Anacardiaceae family. Producing nations that rank high in mangoes include India, China, Thailand, Indonesia, Pakistan, Mexico, Brazil, Bangladesh, Nigeria, and the Philippines. Several phytochemicals in mango leaves have been linked to health benefits, including the antioxidant mangiferin, as well as phenolic acids, benzophenones, flavonoids, ascorbic acid, carotenoids, and tocopherols. The anti-cancer, anti-diabetic, antioxidant, anti-microbial, anti-obesity, lipid-lowering, hepato-protection, and anti-diarrheal properties of mango leaf (ML) extracts have been investigated. Moreover, several types of cancer cell lines (from the liver, breast, prostate, colon, and nasopharynx) have been found to have the cancer-inhibiting effect [11-20]. Very little work has been carried out on the breast cancer models, hence the present study aims to investigate the anti-tumor effect of leaves of *Mangifera indica* on DMBA-induced breast cancer in rats.

Materials and Methods

Chemicals and reagents

DMBA (7, 12-dimethylbenz(a)anthracene) manufactured by Sigma Aldrich, USA, product number D3254-1G, (CAS Number: 57-97-6), lot# PXLNG2901, p code: 1009330344 was purchased from the Scientific chemical store of Patna, Bihar, India. All the other solvents and chemicals used were of analytical grade 99%.

Preparation of *Mangifera indica* leaf ethanolic extract:

The leaves of *Mangifera indica* were collected from the local tree present in the Patna district of Bihar, India. The leaves were identified by a renowned botanist in Patna, Bihar, India. The leaves were shade-dried for 3 days followed by being dried in an incubator at 37°C temperature. Next, the leaves were ground into a powder and soaked in pure ethanol for 48 hours. The resulting ethanolic mixture of leaves was filtered through filter paper to eliminate any remaining solids. Absolute ethanol was used to extract the filtrate after it was transferred to a rota vapor apparatus. After determining the LD_{50} value (4000 mg/Kg body weight), the dosage of ethanolic extract was determined, and the final dose was titrated to 200 mg/kg body weight.

Animals

The animal house at the Mahavir Cancer Sansthan and Research Centre in Patna, India (CPCSEA Registration number. 1129/PO/ReBi/S/07/CPCSEA) kindly provided 24 female Charles Foster rats for this study. Institutional Animal Ethics Committee (IAEC) NO. 2021/1H-06/10/21 authorized the experiments. All procedures involving animal testing were conducted in compliance with the requirements set out by the Committee for Control and Supervision of Experiments on Animals (CPCSEA), New Delhi. Rats were provided with a free-access diet of food and water. Seven days were used for acclimating the rats before the experiments began. The rats used in the experiments were kept in conventional polypropylene cages, with two rats per cage, and were randomly assigned to either a control or treatment group. Rats were kept in an environment with a constant (24 2°C) temperature and a 12-hour light/dark cycle.

Experimental design

Animals (24 female, Charles Foster strain rats), aged 55 to 60 days, weighing around (150 ± 20 g) were classified into 3 groups of n=6 animals each.

Group I- Control group.

Group II- DMBA group - DMBA induced rats only.

Group III- DMBA + *Mangifera indica* group – DMBA-induced rats treated with *Mangifera indica* ethanolic leaf extract (200 mg/kg body weight per day) for 5 weeks after

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tumor development (about 0.8 cm). Ketamine was used to anesthetize the rats at the end of the treatment, and were sacrificed in the diestrous part of their estrous cycle. The rat's blood was obtained by orbital puncture method. Biochemical tests, lipid peroxidation estimates, TNF- estimates were performed on the serum. For the histological analysis, breast tissues were preserved in 10% formalin.

Tumor induction

Female Charles Foster rats (weighting 150 ±10 g) were used to induce tumors in the mammary glands. These rats were 55 days old. Following the protocol of [21] a single dosage of DMBA (7,12-dimethylbenz(a)anthracene) dissolved in olive oil at a concentration of 20 mg/mL was administered intragastrically. Beginning in the fourth week, following DMBA injection, 20 rats were palpated weekly to detect the growth of tumors. By week 20th, all 18 of the rats in the DMBA-treated group had tumors, while the first tumor emerged at week 18.

Evaluation of mammary tumor volume

The volume of breast tumors was determined using a vernier callipers. The tumor's volume (V) was determined using the formula V(cm^3) = (L B2)/2, where L and B are the perpendicular tumor diameters in centimetres (cm).

Haematological parameters study

The acquired blood samples were analysed using conventional methods to determine haematological parameters such as complete blood count, white blood cell count, platelet count, and haemoglobin percentage.

Biochemical assays

The UV - Vis spectrophotometer (UV-10, Thermo Scientific, USA) was used for biochemical analysis following the standard kit technique (Coral crest). [22] the method was used to measure alanine transaminase (ALT) and aspartate transaminase (AST), [23] method was used to measure alkaline phosphatase (ALP), [24] method was used to measure total bilirubin [25-29] methods were used to analyze urea, creatinine, and uric acid, respectively, as kidney biomarker measures.

Lipid peroxidation (LPO)

The twofold heating method [30], which is based on the spectrophotometric assessment of colour reproduction during the reaction of thiobarbituric acid (TBA) with malondialdehyde (MDA), was used to assess TBARS, a marker of LPO. In this experiment, 0.5 mL of serum was combined with 2.5 mL of a 10% trichloroacetic acid (TCA) solution in a centrifuge tube, and the whole thing was heated in a water bath at 90°C for 15 minutes. The mixture was centrifuged at 3000 rpm for 10 minutes after cooling at ambient temperature, and the resulting 2 mL supernatant was combined with 1 mL of 0.675% TBA solution in a test tube before being heated in a water bath at 90°C for 15 minutes. Subsequently, UV-visible spectrophotometer readings were taken at 532 nm (Thermo Scientific UV-10 USA).

Tumor necrosis factor-alpha (TNF- α) assay

Serum TNF- levels were measured with the ELISA technique. Diaclone, a French company, produced a rat TNF- ELISA kit (Cat. No. 872.010.001). According to the manufacturer's instructions and [31], the serum TNF- level was calculated using a Merck ELISA reader.

Histopathology study

Rats' breast tissue was cut into small pieces and fixed in 10% formalin for 24 hours. The tissues were then embedded in paraffin after being dehydrated with ethanol. For histological examination, 5µm sections were cut and stained with haemotoxylin and eosin.

Statistical analysis

The data is shown in a mean and standard error of the mean (SEM) format. Two-way analysis of variance (ANOVA) with time and drug as the two components were used to compare tumor volume between the DMBA group and the DMBA + *Mangifera indica* group. Biochemical, LPO, and hormonal testing results were compared across groups using one-way analysis of variance (ANOVA) and Tukey's multiple comparison tests for statistical significance. Statistical significance was set at $P<0.05$, and the analysis was performed with the help of the GraphPad Prism 5 program (GraphPad Software, Inc., San Diego, USA).

Results

Morbidity and mortality

Each of the six rats exposed to DMBA developed a tumor in the area of their respective mammary teats 1, 2, 3, and 7. The DMBA + *Mangifera indica* group significantly impeded the growth of tumors in the remaining six rats from teats 1, 3, 5, and 6. No deaths were recorded among any of the groups. The DMBA group and the DMBA + *Mangifera indica* group are shown graphically in (Figure 1).

Changes in tumor volume

Tumor volume increased with time in both the DMBA and DMBA + *Mangifera indica* groups. Figure 2 shows that when *Mangifera indica* ethanolic leaf extract was supplemented on DMBA-induced rats the tumor volume was significantly reduced ($p< 0.005$) compared to when DMBA was used alone. As a result, the *Mangifera indica* leaf extract led to a 47% decrease in ultimate tumor volume.

Changes in malondialdehyde (MDA) level

There was a statistically significant ($p< 0.05$) increase in

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malondialdehyde (MDA), a measure of lipid peroxidation, between the DMBA group and the control group. However, compared to the DMBA group, the MDA level decreased considerably ($p< 0.05$) in the DMBA + *Mangifera indica* group (Table 1.).

Changes in TNF- α levels

The serum TNF- level was significantly higher in the DMBA-treated group compared to the control group ($p<0.05$). The serum TNF- level was lower in the DMBA + *Mangifera indica* group compared to the DMBA group ($p<0.05$) (Table 2).

Haematological parameters Study

According to the results of the haematological analysis, the red blood cell count, white blood cell count, platelet count, and haemoglobin percentage were all significantly decreased in the DMBA-treated rats compared to the control group rats but were significantly normalized in the *Mangifera indica* leaf extract-treated rats ($p<0.05$) (Table 3).

Changes in liver and kidney serum biomarker parameters

Serum total bilirubin, ALT, and ALP levels were all substantially ($p<0.05$) higher in the DMBA group compared to the control group. Serum total bilirubin, ALT, AST, and ALP levels were all considerably lower in the DMBA + *Mangifera indica* group compared to the DMBA group ($p<0.05$) (Table 4). Serum creatinine, urea, and uric acid levels were all significantly ($p<0.05$) higher in the DMBA group compared to the control group, suggesting renal damage. Serum creatinine, urea, and uric acid levels were considerably decreased ($p<0.005$) in the DMBA + *Mangifera indica* group compared to the DMBA group (Table 4).

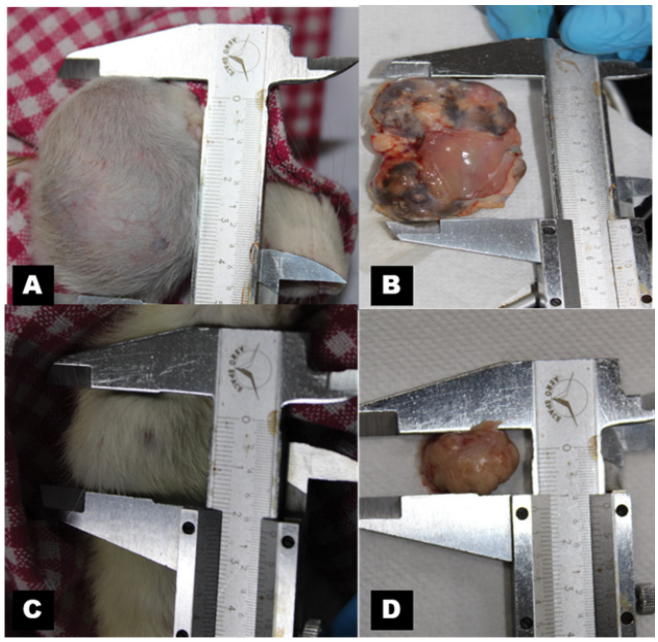

Figure 1: Gross photographs of rat mammary tumor, 1A & 1B of DMBA group (single dose of DMBA at 20 mg/mL in olive oil) and 1C & 1D of DMBA + *Mangifera indica* group. *Mangifera indica* was administered at the dose of 200 mg/kg body weight per day for 5 weeks after about 0.8 cm tumor development).

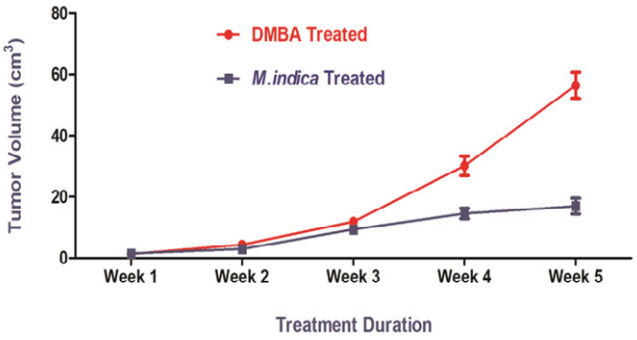

Figure 2: Effect of different treatments on tumor volume in the studied groups. DMBA group (single dose of DMBA at 20 mg/mL in olive oil), DMBA + *Mangifera indica* group (*Mangifera indica* at 200 mg/kg body weight per day for 5 weeks after about 0.8 cm tumor development). Values are expressed as mean ± SEM, n=6)

Table 1: Levels of Lipid Peroxidation in different treatment groups

Parameters	Control	DMBA Treated	*Mangifera indica* Treated
Lipid Peroxidation	2.59 ± 0.94	205.53 ± 7.38	10.23 ± 2.43

Table 2: TNF alpha levels in different treatment groups

Parameters	Control	DMBA Treated	*Mangifera indica* Treated
TNF alpha (pg/mL)	7.41 ± 0.23	98.75 ± 3.22	20.5 ± 2.12

Table 3: Haematological parameters

Parameters	Control	DMBA Treated	*Mangifera indica* Treated
RBC Count ($\times 10^6$ mm $^{-3}$)	7.4 ± 1.5	2.53 ± 0.95	7.2 ± 2.83
WBC Count (mm $^{-3}$)	9400 ± 4.7	16000 ± 4.3	8700 ± 2.55
Platelets counts ($\times 10^6$ mm^{-3})	1.9 ± 0.67	0.78 ± 0.83	2.5 ± 0.92
Haemoglobin (g/mL)	13.7 ± 1.36	7.4 ± 2.45	13.1 ± 3.76

Histopathological findings

In the present histopathological examination Figure 3A, the mammary tissue section of the control rat, shows normal architecture of mammary tissue. The DMBA group rat shows a mammary tumor section in Figure 3B. Both mesenchymal and epithelial cells are involved in this, so it is a mixed mammary gland tumor. Its papillary projections, cystic dilatation, cellular sheet formation, pleomorphic, etc together with patches of embryonic mesenchymal cells confirm the

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Tubulo-papillary carcinoma of the breast in rats. The DMBA + *Mangifera indica* group rat shows a mammary tumor section in Figure 3C. In these sections, there is a regression in the tumour cells.

Table 4: Biochemical Parameters Study

Parameters	Control	DMBA Treated	*Mangifera indica* Treated
SGPT (U/mL)	30.12 ± 2.2	201.57 ± 3.47	40.5 ± 3.14
SGOT (U/mL)	28.86 ± 1.6	230.78 ± 6.34	43.2 ± 2.12
ALP (KA units)	4.67 ± 1.78	50.12 ± 2.46	7.56 ± 1.24
Urea (mg/dL)	30.55 ± 1.89	72.12 ± 4.93	37.22 ± 1.78
Uric acid (mg/dL)	4.14 ± 1.20	14.14 ± 1.45	9.24 ± 3.56
Creatinine (mg/dL)	0.84 ± 0.49	4.17 ± 1.23	1.25 ± 1.12

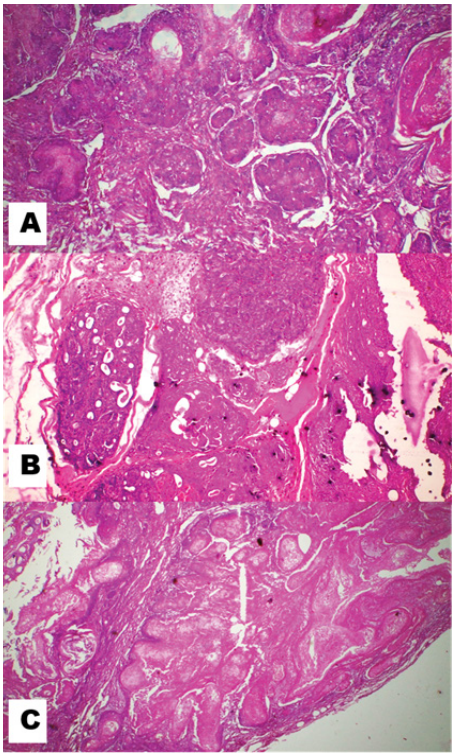

Figure 3: Microphotograph of rat mammary tissue stained with haematoxylin and eosin. (A) Section of control rat mammary tissue showing the normal arrangement of adipocytes and lobules x200. (B) The mammary tissue section of the DMBA group rat showing papillary projections, cystic dilatation, cellular sheet formation, pleomorphic, etc. together with patches of embryonic mesenchymal cells confirms the Tubulo-papillary carcinoma of breast x500. (C) The mammary tissue section of DMBA + *Mangifera indica* leaf-treated group rat showing mature fibrous tissues indicates tumour regression process x500.

Discussion

DMBA is converted into the ultimate carcinogen DMBA-3,4-dihydrodiol-1,2-epoxide (DMBA-DE) by metabolic activation by the cytochrome p450 enzyme. Tissue redox equilibrium is disrupted due to the production of several reactive oxygen species (ROS) during metabolic activity. These reactive species promote malondialdehyde (MDA) production, a byproduct of lipid peroxidation (LPO). In both animal models of cancer and human cancer patients, high levels of MDA have been universally regarded as an indicator of oxidative stress and antioxidant status. Serum MDA levels were found to be significantly higher in the DMBA group compared to the control group in the current investigation. However, compared to the DMBA group, serum MDA levels decreased markedly in the DMBA+ *Mangifera indica* group. *Mangifera indica* ethanolic leaf extract's antioxidant capacity may be shown in its ability to lower levels of malondialdehyde (MDA). The primary phytochemical elements of *Mangifera indica* are responsible for its antioxidant action. As redox imbalance leads to unchecked cellular growth, the antioxidant potential may have helped preserve the redox condition of the cells, which is often disrupted by carcinogen metabolism. Mangiferin is a polyphenolic antioxidant and a glucosyl xanthone with significant antioxidant, anti-lipid peroxidation, immunomodulatory, cardiotonic, hypotensive, wound healing, antidegenerative, and antidiabetic actions, making it an important pharmacological and therapeutic chemical [32-34]. During the carcinogenic process induced by DMBA, the pro-inflammatory cytokine tumor necrosis factor (TNF) is expressed at higher levels, and NF-kB (nuclear factor-kB), a transcription factor involved in the survival and proliferation of neoplastic cells, is translocated into the nucleus via a TNF mediated increase. Elevated levels of TNF play a critical role in driving the development of breast cancer. Serum TNF levels were found to be significantly higher in the DMBA group compared to the control group in the current investigation. However, compared to the DMBA group, the serum TNF level was considerably lower in the DMBA+ *Mangifera indica* group. *Mangifera indica* ethanolic leaf extract's anti-inflammatory effects are shown by a lower blood TNF level. Cho et al. similarly noticed a decrease in TNF levels. Mangiferin's anti-proliferative effects on T cells have also been shown to play a vital role in controlling cell proliferation [35-38]. Despite a trend toward a smaller breast tumor volume in the DMBA + *Mangifera indica* group compared to the DMBA group at the study's end, the difference was not statistically significant. However, a maximum of 47% tumor growth inhibition was also detected in the last week of therapy, and it is highly conceivable that there would have been a large drop in the mammary tumor volume of the medicinal plant-treated group if treatment could have been extended for a longer time. Even though there are several effective anticancer medications now in use,

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many of them have major side effects that may affect a wide variety of bodily systems, including severely impairing liver and kidney function. It is crucial, therefore, to evaluate the effect of *Mangifera indica* leaf extract on the functioning of crucial organs including the liver and the kidney. The liver is the principal site where xenobiotic chemicals like DMBA are processed during detoxification. The liver damage and oxidative stress both resulted from the metabolism of the chemical carcinogen. Serum levels of ALT, AST, and ALP were found to be significantly higher in the DMBA group compared to the other two groups. An indicator of liver deterioration is an elevated serum biomarker for hepatitis. But, compared to the DMBA group, the blood total bilirubin, ALT, AST, and ALP levels were considerably lower in the DMBA + *Mangifera indica* group. *Mangifera indica* ethanolic leaf extract has hepatoprotective properties, as shown by the decreased serum levels of liver biomarker measures in the DMBA + *Mangifera indica* group. Similar studies on other models have been well documented [39-42].

The kidney is a crucial organ that not only eliminates harmful byproducts of metabolism but also produces essential chemicals. Consequently, chemotherapeutic drugs may have higher systemic toxicity due to renal impairment, since their excretion and metabolism may be slowed. Serum levels of kidney biomarkers urea, creatinine, and uric acid were all found to be significantly elevated in the DMBA group. The nephrotoxic effects of DMBA are shown by the increased kidney biomarker level. Serum renal biomarkers including urea, creatinine, and uric acid all decreased to a much greater extent in the DMBA + *Mangifera indica* group than in the DMBA group alone. *Mangifera indica* leaf extract's beneficial benefits against DMBA-induced renal damage in rats are seen in the rapid restoration of serum kidney biomarker levels as well. Similar studies on other models have been well documented [43-48]. *Mangifera indica* ethanolic leaf extract has been shown to have anti-proliferative effects in a histopathological examination. Mammary tissue sections from the DMBA group revealed characteristics consistent with tubular-papillary carcinoma of the breast, including papillary projections, cystic dilatation, cellular sheet development, pleomorphic, and patches of embryonic mesenchymal cells, indicating a more rapid tumor growth rate. Most of the fibrous tissues in the DMBA + *Mangifera indica* group are mature, which is indicative of a slower tumor development rate. The ultimate tumor volume of the two-treatment group was measured, further confirming the antiproliferative characteristics. Similar, studies on other models have been well documented by [49, 50, 51].

Conclusion

All this evidence implies that the ethanolic leaf extract of *Mangifera indica* has antitumorigenic properties, particularly in its ability to fight free radicals. The plant extract also protects the liver and kidneys. Therefore, it is reasonable to infer that the plant extract has a preventative and curative function in preventing DMBA-induced breast cancer in rats. There is also promising research into using an ethanolic extract of *Mangifera indica* leaf as a chemotherapeutic agent for the treatment of breast cancer. Furthermore, studies are recommended to get the molecular mechanism and mode of action of leaf extract of *Mangifera indica*. However, the present study appears to have a promising role in controlling breast cancer in DMBA-induced rat models.

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Author Contributions:

Design of experiments and preparation of manuscript (Jyoti Prakash, Chandrajeet Kumar, Arun Kumar). Conducted laboratory studies (Jyoti Prakash, Aparna Jyoti Kujur and Arun Kumar). Microphotography and interpretation were done by Sanjiv Kumar. Proofreading of the manuscript (Jyoti Prakash, Chandrajeet Kumar, Sanjiv Kumar, Aparna Jyoti Kujur, Arun Kumar). All authors read and approved the final manuscript.

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Declaration of conflicting interests

The authors declare that they have no conflict of interest.

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