IJPSR (2025), Volume 16, Issue 6 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 30 December 2024; received in revised form, 05 February 2025; accepted, 14 February 2025; published 01 June 2025

EFFECT OF METHANOLIC EXTRACT OF *PLUMERIA PUDICA* JACQ. LEAVES AGAINST DMBA-INDUCED MAMMARY CARCINOMA IN RATS

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Keywords:

Plumeria pudica, DMBA, Pre-Treatment, Post-Treatment, Mammary Tumor

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ABSTRACT: Background: Breast cancer is the most occurring cancer in women and the second most reason for tumour related deaths in women. Chemoprevention, which involves employing dietary, natural, or synthetic items, has emerged as an intriguing strategy to deal with increase in Breast cancer cases. *Plumeria pudica* Jacq. is fast growing, having medium size and belongs to the family Apocynaceae. The high concentration of phenols and phenolic chemicals in *P. Pudica* suggests that it may be utilised to cure cancer. **Materials and Methods:** In present study, mammary carcinoma was induced in female wistar rats by intragastric (IG) administration of 7, 12-dimethylbenz[a] anthracene (DMBA) at a dose of 80mg/kg of body weight. Treatment of methanolic extract of *plumeria pudica* leaves (200mg/kg/BW, thrice a week) to breast tumor bearing rats was found to be effective against DMBA induced mammary carcinoma. Progression of mammary carcinoma associated with decrease in body weight, anaemia, leucocytopenia, elevated levels of tumorigenicity, increase in oxidative stress and increased Liver biomarker levels. **Result:** The study showed the ability of various phytoconstituents present in *Plumeria pudica* in enhancement of body weight, decrease in tumorigenic parameters, and restoration of haematological function with hepatoprotective effect. **Conclusion:** From overall study, we can say that the pre-treatment with *Plumeria pudica* has showed Chemopreventive effect in DMBA induced mammary carcinoma in rats. These findings demonstrate the preventive role of *Plumeria pudica* in DMBA induced mammary carcinoma in rats.

INTRODUCTION: Cancer is a multidimensional genetic disease that results in body's abnormal cells multiplying and dividing out of control, spreading to other body tissues [1]. Accordance to American Cancer Society, Mammary carcinoma is the most common cancer in women and 2nd highest reason for tumor-related deaths in women.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.16(6).1684-91

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(6).1684-91

Every year, there are more new instances reported, and compared to other tumors, the likelihood that a woman will develop breast cancer is extremely high (1:8) [2]. Due to first-line drug resistance, a high chance of relapse, and spread of metastatic disease [3].

More than 60% of the anticancer medications in use today come from natural sources. Chemoprevention, which involves employing dietary, natural, or synthetic items, has emerged as an intriguing strategy to deal with the rising incidence of breast cancer [4]. The United States FDA has currently approved tamoxifen and

raloxifene as SERMs (selective oestrogen receptor modulators) for the chemoprevention of carcinoma of the breast in women who are extremely vulnerable. However, there are worries about the possible side effects, which restricts the frequent and long-term use of these medications. Additionally, it's conceivable that the effects of these medications won't completely lower your chance of developing breast cancer [5]. Now-a-days chemical compounds are being used to induce breast carcinoma in rats and mice. The DMBA belongs to the class of PAHs, which is a carcinogenic substance [6]. The DMBA induced mammary carcinoma resembles with IDC type of carcinoma in humans. Since mammary tissues are abundant in fat tissues and DMBA has a high lipophilicity, it accumulates there after administration [7]. It disturbs DNA repair through depurination and also causes oxidative stress, this results in growth of tumours and inhibition of cell death pathways in the tissues. So, DMBA was used as carcinogen to induce mammary carcinoma in rats [8]. Chemoprevention, which involves employing dietary, natural, or synthetic items, has emerged as an intriguing strategy to deal with the rising incidence of breast cancer [9, 10]. *Plumeria pudica* Jacq. is fast growing, having medium size and belongs to the family Apocynaceae [11]. *Plumeria pudica* methanolic leaf extract contains alkaloids, carbohydrates, glycosides, tannins, phenols, flavonoids, terpenoids, steroids, oils cardiac glycosides and fats and proteins [11, 12]. This demonstrates how much more effectively the methanolic extract can extract secondary metabolites [13]. As per study done by Nainesh Modi *et. al*, TPC in the ME of *P. pudica* was 248.3 ± 3.33 mg GAE/g of sample, while TFC was found to be 108.3 ± 1.67 mg QE/g of sample. The DPPH assay of ME of *P. pudica* was done by Nainesh Modi *et. al*, which showed that *P. pudica* leaf extract demonstrated strong free radical scavenging activity, which may be related to the presence of flavonoids and phenolic substances. The greater amount of phenolic compounds and flavonoid contents, indicated that this plant has strong antioxidant properties. The high concentration of phenols and phenolic chemicals in *P. pudica* suggests that it may be utilised to cure cancer [14].

FIG. 1: PLANT OF *PLUMERIA PUDICA*

FIG. 2: LEAF OF *PLUMERIA PUDICA*

MATERIALS AND METHODS:

Chemicals: DMBA was purchased from Alfa Aesar, Thermo Fisher Scientific India Pvt. Ltd. (Powai).corn oil was purchased from Eywa seeds and exports private Ltd. (Jamnagar). All other chemicals used in study were of analytical grade.

Animals: The experiment was conducted at the animal house of pharmacology department, A.B.C. P. Sangli. The experiment was done according to the CPCSEA guidelines. Wistar female Rats weighing 160-200 gm was used. The animals were chosen randomly & placed on bedding throughout the experiment in cages containing sterile husk having free access to food & water. Approval for animal study has been taken by IAEC and IAEC approval number is IAEC/ABCP/05/2022-23.

Collection and Authentication of Plant: The leaves of *plumeria pudica* were collected from Ganesh nursery, Sangli in the month of December 2022 to January 2023. The plant was authenticated by Dr. M.D Wad mare, associated professor and head of department of Botany at Kasturbai Walchand College, Sangli.

Processing and Extraction: The leaves were washed with distilled water and shade dried in sun. The leaves were ground to coarse-fine powder by using morter pestle and passed through sieve

number 40. The weighed quantity of powder was extracted with methanol using Soxhlet apparatus at 65°C. Obtained extract was dried at room temperature.

Study Design for *In-vivo* Study [15]: Total 30 rats were randomly selected and allotted to five groups each containing six rats. The groups and respective treatments are as follows:

- **Group-I: Vehicle Control:** Rats were administered Corn oil (Thrice a week) – For 12 weeks
- **Group-II: DMBA Control:** Mammary tumors were induced by Single dose of DMBA (80mg/kg in 0.5ml corn oil) in third week and corn oil from week 4-12.
- **Group-III: Drug Control:** Rats were administered *P. pudica* extract (200mg/kg) orally –Thrice a week for 12 weeks
- **Group-IV: *P. pudica* Pre-treatment:** Animals were subjected to pre-treatment with *P. pudica* (200mg/kg) *P. pudica* extract orally – Thrice a week for 12 weeks and DMBA (80mg/kg in 0.5ml corn oil) administration in third week.
- **Group-V: *P. pudica* Post-treatment:** Animals were subjected to post-treatment with *P. pudica* (200mg/kg) *P. pudica* extract orally from week 8 and DMBA (80mg/kg in 0.5ml corn oil) administration in third week.
- All animals were sacrificed at end of 12 weeks and Evaluation was done by using appropriate methods.

Body Weight of Animals: Body weight of all animals were recorded once in week for 12 weeks.

Tumor Parameters: Tumor yield, Tumor Volume [16], Tumor Burden [17], Tumor size and Tumor mass were evaluated for study [18].

Hematological Parameters: All Hematological parameters Hb, RBC, WBC and DLC were evaluated at interval of two weeks [19].

Tissue Antioxidant Biomarkers: Tissue antioxidant biomarkers of breast tissue Superoxide dismutase (SOD) and Glutathione Reductase (GSH) were determined by using by Marklund *et.al* method and by Ellman *et.al* method respectively.

Liver Parameters: SGOT and SGPT of liver tissue of animals were measured by using Modified IFCC method [20].

Statistical Analysis: All Values are expressed as Mean ± SEM for six rats in each group. Statistical analysis test was done by using One-way Anova followed "Dunnett's multiple comparisons test" by using Graph Pad Prism software (8.00, USA) All the data is compared with DMBA Control group.

RESULTS:

Effect of *Plumeria pudica* Extract on Body Weight:

TABLE 1: EFFECT OF *PLUMERIA PUDICA* EXTRACT ON BODY WEIGHT

Sr. no.		Vehicle control	Drug Control	DMBA Control	Pre – treatment	Post-treatment
1.	Body weight (grams)	165.7361± 1.408975****	161.6389± 1.616913****	142. 1389± 3.506234	151.4028± 3.091964*	147.2639± 2.375478*

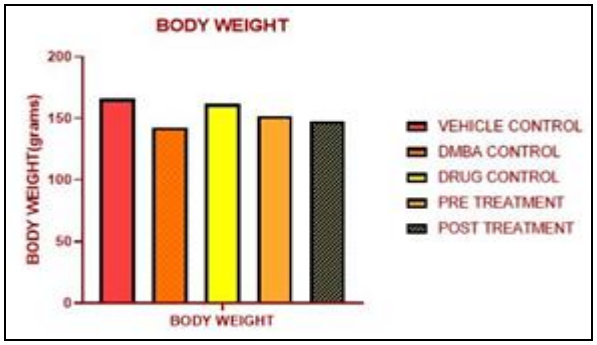


FIG. 3: EFFECT OF *P. PUDICA* ON BODY WEIGHTS OF ANIMALS

Tumor Parameters:

TABLE 2: TUMOR PARAMETERS

Parameter	DMBA Control	Pre- Treatment	Post-Treatment
Tumor Volume (cm^3)	4.4265 ± 0.331815	0.853167 ± 0.097613****	2.264667 ± 0.36824***
Tumor Burden (%)	6.19 ± 0.013944	1.19 ± 0.002733****	2.66 ± 0.005247****
Tumor Mass (Grams)	5.7 ± 0.444222	2.05 ± 0.321196****	4.26667 ± 0.207632**
Tumor Yield	1.66667 ± 0.210819	1.166667 ±0.166667	1.33333 ±0.210819
Tumor Size (cm)	5.31 ± 0.505688	1.586667 ± 0.112862****	3.04 ± 0.304926***

(A) DMBA Control group (B) Pre-Treatment Group (C) Post-Treatment Group

FIG. 4: TUMORS ISOLATED FROM A) DMBA CONTROL GROUP B) PRE-TREATMENT GROUP C) POST-TREATMENT GROUP

Haematological Parameters:

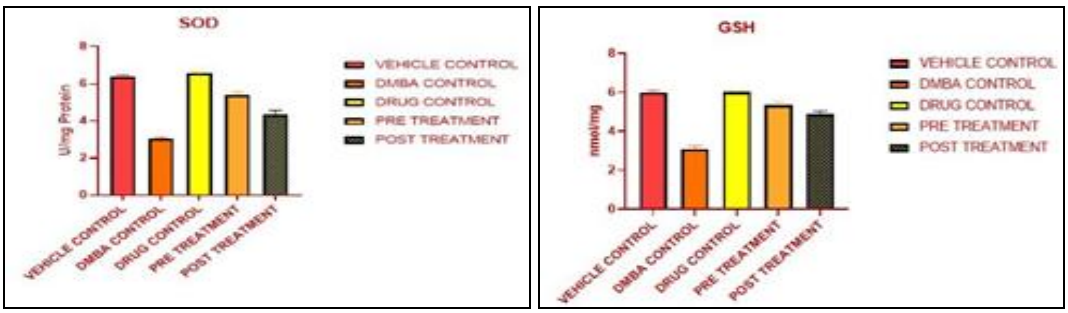
TABLE 3: HAEMATOLOGICAL PARAMETERS

		Haematological Parametres				
Sr. no.	**Parameter**	**Vehicle Control**	**DMBA Control**	**Drug Control**	**PRE Treatment**	**Post Treatment**
1	Hb (gm/dl)	13.46389± 0.285202****	10.26389 ± 0.639285	14.04167 ± 0.220386****	12.58611± 0.527205*	11.65278± 0.214982**
2	RBC (millions/cumm)	7.802778± 0.095465****	6.1± 0.083307	7.85555± 0.122161****	6.825± 0.180684**	6.661111 ± 0.253899*
3	WBC (thousands/cumm)	7608.889 ± 101.5566****	5577.778± 62.075	7562.222± 60.4933****	6121.11± 76.3438**	5800.111± 76.730*
4.	Lymphocytes (%)	60 ± 1.247219****	41.57143 ± 0.996024	62.14286 ± 1.300183****	52.71429 ± 1.40859****	46.14286± 0.684291*
5.	Neutrophils (%)	19.57143 ± 1.868706**	10 ± 1	21.42857 ± 2.119449***	17.71429± 2.207491**	14 ± 0.881917*

Antioxidant Biomarkers:

TABLE 4: RESULTS OF ANTI-OXIDANT BIOMARKERS

Parameter	Vehicle Control	DMBA Control	Drug Control	Pre-Treatment	Post-Treatment
SOD (U/mg protein)	6.366667 ± 0.120185****	3.066667 ± 0.054536	6.55 ± 0.125831****	5.4 ± 0.169312****	4.355 ± 0.216852****
GSH (nmol/mg)	5.983333 ± 0.11949****	3.076667 ± 0.178245	6.016667 ± 0.11949****	5.35 ± 0.162788****	4.88333 ± 0.157938****



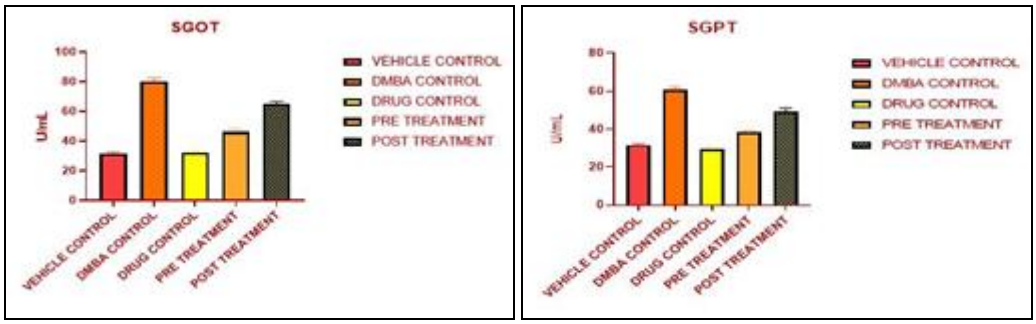
(A) SOD Level (B) GSH level

FIG. 5: EFFECT OF *P. PUDICA* EXTRACT ON SOD LEVEL AND GSH LEVEL

Liver Biomarkers:

TABLE 5: RESULT OF LIVER BIOMARKERS

Parameter	Vehicle Control	DMBA Control	Drug Control	Pre-Treatment	Post-Treatment
SGPT (U/mL)	31.66667 ± 0.557773****	60.5 ± 1.688194	29.5 ± 0.846562****	38.16667 ± 1.194897****	49 ± 2.175623****
SGOT (U/mL)	31.5 ± 1.176152****	80.33333 ± 2.155097	32.33333 ± 1.47573****	46.16667 ± 2.242271****	65 ± 2.175623****



(A) SGOT level **(B) SGPT level**

FIG. 6: EFFECT OF *P. PUDICA* EXTRACT ON SGOT LEVEL AND SGPT LEVEL

DISCUSSION: Chemoprevention, which involves employing dietary, natural, or synthetic items, has emerged as an intriguing strategy to deal with the rising incidence of breast cancer. Flavonoids are powerful antioxidants that can shield cells from cellular oxidation, damage, and cancer [16]. The greater amount of phenolic compounds and flavonoid contents, indicated that this plant has strong antioxidant properties. The acute toxicity study of methanolic extract of leaves of *plumeria pudi*ca was done according to OECD guideline - 423. The LD50 was found to be 2000mg/kg and extract showed it was safe to administer in rats, so 1/10th dose200mg/kg was selected for animals' study.

The body weight of animals in DMBA control group was significantly reduced as the progression of disease. Weight loss and declining body condition, diarrhea, progressive dermatitis, respiratory-related symptoms such laboured breathing and impairment of access to food and water were the physical alterations seen in the DMBA control group [21]. In pre-treatment group, After the DMBA induction in third week body weight was significantly reduced from week 5 but from week 8 there was slight increase in body weight of animals and up to week 12 there was significant increase in body weights of animals. In post-treatment group the weight was significantly reduced from week 5but from week 11 there was slight increase in body weight of animals. The body weight of animals in pre-treatment group was increased as there is presence of phytoconstituents such as α -pinene, γ -terpinene, eugenol, and d-limonene which are proven to be nutrients in nature and may be responsible for enhancement in body weights. Tumor volume, Tumor Burden, Tumor size and Tumor mass was highest in DMBA control group. Tumor volume, Tumor Burden, Tumor size and Tumor mass was significantly decrease in Pre-treatment group of animals as they are provided the *Plumeria pudica* extract throughout 12 weeks. Tumor volume, Tumor Burden, Tumor size and Tumor mass was slightly reduced in post-treatment group as compared to DMBA control group. The pre-treatment with *Plumeria pudica* showed effective result against DMBA induced Breast cancer.

As per GC-MS the phytoconstituents that are responsible for inhibition of tumor growth and progression may act by following mechanism- α -pinene can suppress the expression of Matrix metalloproteinase-9, which inhibits malignant invasion [22]. Limonene may inhibit the expression of the protein cyclin D1 in breast tumours [23], which may result in cell-cycle arrest and reduced cell growth. Apoptosis may be triggered by phenyl acetaldehyde, which also successfully suppresses colony formation, migration, and proliferation [24]. Citronellal may inhibit cancer cell proliferation by

triggering apoptosis [25]. Hexadecanoic acid may boost the production of caspase-3, caspase-8, and Bax proteins to inhibit proliferation and promote death [26]. The growth of mammary gland tumors can be slowed by phytol [27].

The Hematological parameters of each group of animals are evaluated once in two weeks. As there is cancer progression, myelosuppression and anaemia occur as response to cancerous cell. The Hb level, RBC count and WBC count was moderately decreased in DMBA control group and in pre-treatment group there was increase in Hb level, RBC count and WBC count. The slight increase in Hb level, RBC Count and WBC count was observed in animals of post-treatment group. The pre-treatment with *Plumeria pudica* showed satisfactory increase in Hb level, RBC count and WBC count which demonstrate that there is less chances of myelosuppression and anemia in treatment of cancer. The Hb level, RBC count an WBC count in Drug control and Vehicle group was found within Normal Limits which indicate that there is no adverse effect of drugs on Haematological Parameters.

Antioxidants can stop damage caused by reactive oxygen species. Superoxide dismutase, an antioxidant enzyme, is essential for cellular defence against free radical damage. GSH is a chain-breaking antioxidant that scavenges free radicals to stop polyunsaturated fatty acids from becoming oxidised, which can encourage the development of cancer [28, 29]. The SOD level in DMBA Control group was found to be low. There was significant increase in SOD level in Pre-treatment and Post-treatment group of animals as compared to DMBA control group. The GSH level in DMBA Control group was found to be low. There was significant increase in GSH level in Pre-treatment and Post-treatment group of animals as compared to DMBA control group. The SOD and GSH levels in Vehicle Control group and Drug control group was found within normal limits. The rise in SOD and GSH levels, which may be brought on by the presence of flavonoids and phenolic substances. The greater amount of phenolic compounds and antioxidant activity indicated that this plant has strong antioxidant properties. Terpinolene, γ-Terpinene, Limonene and Geraniol present in extract possesses antiproliferative and antioxidant effects, which may be involved in protecting the cells from oxidative damage and restoration of antioxidant actions [30, 31]. The mutagenic and carcinogenic effects of DMBA depend on metabolic activation. The liver is the primary site for metabolism of DMBA. The liver damage is believed to be caused by the carcinogenic metabolites and ROS produced as a result of DMBA metabolism [32]. There were significant higher levels of SGPT and SGOT in DMBA control group which indicates there is liver damage caused by DMBA. There was significant decrease in SGOT and SGPT level in pre-as compared to DMBA control group. The SGOT and SGPT levels in Drug control group and Vehicle control group was found to be within normal limits. Flavonoids and phenols present in extract may exert hepatoprotective effects by regenerating the damaged portions of the liver. The levels of SGOT and SGPT levels significantly decreased in Pre-treatment group which indicate that extract lowers hepatic damage and restore the normal functions of liver. The observed reduction in the serum liver biomarker levels was indicative of the hepatoprotective effect of extract.

CONCLUSION: The study showed that DMBA at a dose of 80mg/kg induced mammary carcinoma in wistar rats. The progression of mammary carcinoma associated with decrease in body weight, anaemia, leucocytopenia, elevated levels of tumorigenicity, increase in oxidative stress and increased liver biomarker levels. From the results, it is evident that Pre-treatment with *Plumeria pudica* is capable of protecting against oxidative damage. Further, the study showed the ability of various phytoconstituents present in *Plumeria pudica* in enhancement of body weight, decrease in tumorigenic parameters, and restoration of haematological function with hepatoprotective effect. From overall study, we can say that the pre-treatment with *Plumeria pudica* has showed chemopreventive effect in DMBA induced mammary carcinoma in rats.

ACKNOWLEDGMENT: The authors are acknowledging gratefulness to Department of Pharmacology, Appasaheb Birnale college of Pharmacy for Laboratory facilities and guidance.

CONFLICTS OF INTEREST: The authors declare no conflict of Interest.

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How to cite this article:
Jamadar AG and Naikwade SNS: "Effect of methanolic extract of *Plumeria pudica* Jacq. leaves against DMBA-induced mammary carcinoma in rats". Int J Pharm Sci & Res 2025; 16(6): 1684-91. doi: 10.13040/IJPSR.0975-8232.16(6).1684-91.