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ANTI-TUMOR ACTIVITY OF *TARAXACUM OFFICINALE* LAM. LEAVES AGAINST DMBA-INDUCED SKIN CANCER IN SWISS ALBINO MICE

Madan Lal Kaushik, Manpreet Singh, Deepika Rani * and Ranjit Singh

Adarsh Vijendra Institute of Pharmaceutical Sciences, Shobhit University, Gangoh, Saharanpur - 247341, Uttar Pradesh, India.

Keywords:

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Correspondence to Author:
Deepika Rani

Associate Professor,
Adarsh Vijendra Institute of Pharmaceutical Sciences,
Shobhit University, Gangoh,
Saharanpur - 247341, Uttar Pradesh, India.

E-mail: deepikapharma94@gmail.com

ABSTRACT: Objective: To investigate the antitumor activity of different extracts (petroleum ether, ethanolic and aqueous extracts) of *Taraxacum officinale* against DMBA-induced skin cancer in mice. **Methods:** *T. officinale* leaves were successively extracted using petroleum ether (PTO), ethanol (ETO) and water (ATO). The antitumor activity was evaluated against DMBA-induced skin cancer in swiss albino mice. The morphological and biochemical parameters were observed inrelation to the skin papilloma. **Results:** PTO, ETO and ATO were administered at dose of 200 mg/kg body weight, respectively to DMBA-induced skin cancer in mice. All the treatment groups showed a significant ($P < 0.05$) improvement in all biochemical parameters by restoring to the normal level. The morphological study confirmed that the treatment groups showed a significant reduction in tumor size and the tumor number compared with group II. ETO extract was found to be highly effective against DMBA-induced skin cancer in mice as compared to PTO & ATO groups. **Conclusion:** The results were significant and confirmed that the *T. officinale* ETO extract has remarkable antitumor activity against DMBA Induced skin cancer in mice.

INTRODUCTION: Skin cancer (SC) is the destructive growth of abnormal skin cells on that part which is excessively exposed to sun's carcinogenic UV-radiations. Its incidence is increasing rapidly day by day all over the world [1-3]. SC is basically characterized in two types melanotic and non-melanotic type [4], among these non-melanotic skin cancer (NMSC) is quite prominent [5], with a rate of an incident of 95% of all SC and comprising 40% of all malignancies worldwide [6]. Melanocytic skin cancer is a highly destructive life-threatening disease and mostly seen in populations of white races [7].

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The major cause of this is the invariant expression of MC1R gene on over-exposure to UV radiations [8]. MC1R gene is primarily responsible for producing eumelanin, a pigment that protects against the carcinogenic effect of UV radiations [9, 10]. Apart of this, other important genetic drivers are B-Raf proto-oncogene (BRAF), neuroblastoma RAS viral (v-ras) oncogene (NRAS) mutations, and neurofibromin 1 (NF1) [11, 12]. NMSC is the most common type of SC comprising basal cell skin carcinoma and squamous cell skin carcinoma with an incidence rate of 70% and 25%, respectively [13].

This type of malignancy is quite common in white races, especially in age [14] and its incidence is increasing day by day [15] with a low mortality rate. Although it's current statistics is unclear [16]. The major cause of NMSC is over-exposure to Ultra violet radiations (UVR) i.e. UVA and UVB 17, which are responsible for 90% of NMSC. The overexposure to UVR may activate various tumors

causing gene (oncogenes) while suppressing the protective genes, causing mutation in DNA or causing apoptosis in keratinocytes [18, 19]. Different types of mutations in the DNA or gene may responsible for NMSC such as mutations in the PTCH tumor-suppressor gene 1 [18], p53 [20] and p16INK4A genes, Brahma (BRM) and the Brahma-related gene 1 protein (BRG1) [21], ras oncogene [22] and in Phosphatase tensin homolog (PTEN) [23].

The basic recommendation to prevent SC is to avoid mutagenesis, its primary cause. However, conventional treatment involves the surgical removal of malignant tissue followed by chemotherapy which poses a huge health burden on patient [24]. So, the interest in alternative medicines has been increasing day by day. Natural phytoconstituents (NP) derived from different sources *i.e.,* plant; marine, and animal, are most widely used as an alternative for treating SC. NP may adopt different mechanisms for their anti-cancer effect, such as inducing apoptosis or suppressing the effect of tumor-inducing proteins [25]. Recently Federal drug administration and European Medical agency approved aningenol mebutate topical gel having extracts of Euphorbia for the treatment of actinic keratosis [26].

The leaves of *T. officinale* Lam, most commonly known as dendilions were used in the present study for the determination of their anticancer potential against DMBA-induced skin cancer. Various studies reported the presence of saponins, phenolic compunds, sesquitriterpenes, triterpenes, tannins and reducing sugar in both aqueous and ethanolic leaf extracts of *T. officinalis* [27, 28].

MATERIALS AND METHODS:

Plant Material: The leaves of *T. officinale* were collected from Kashmir, India, during the month of January 2019 and were identified by the taxonomist at National Institute of Pharmaceutical Education and Research S.A.S., Nagar, Mohali, Punjab, India with a voucher specimen number of 0016. The plant in maintained in our institutional laboratory for future use.

Chemical and Reagents: DMBA and croton oil (skin cancer inducer and promoter) were purchased from Sigma Co. (St. Louis, MO, USA). The estimation kits such as Catalase, Reduced Glutathione (GSH), Superoxide dismutase (SOD), Lipid Peroxidation (LPO), and Total protein have been purchased from Mark, Bombay, India. The study's other chemical and regents were of the highest analytical grade.

Preparation of Crude Plant Extract: The leaves of *T. officinalis* were shade-dried and then milled to convert it to powder form. Size separation was carried out by passing the powder to sieve number 40 and stored in an air-tight container until further use. About 700 g of powdered leaves were subjected to successive Soxhlet extraction using three different solvents in their increasing order of polarity viz. petroleum ether, ethanol, and aqueous. Each extract was concentrated by distilling off the solvent and then evaporating to dryness using a vacuum rotator evaporator [29].

Animals Activity:

Animals: Healthy adult Swiss albino mice of either sex with age between 2-5 months and a standard weight of 25-30g, were procured from Panacea Biotec Ltd, Lalru (140501), India, and housed in a polypropylene cage. All animals were maintained under standard laboratory conditions at a temperature of 25±2^{o}C with 12/12h night/dark cycle and fed with a standard pellet diet and water ad libitum. The protocol for the study was approved by the institutional animal ethical committee (IAEC) under the guideline approved by the Committee for Control and Supervision on Experimental Animals (CPCSEA), Ministry of Environment and Forests, New Delhi. [protocol no.: IAEC-CTIPS/2018/X/0060 (PCL-M)].

Acute Toxicity Study: The acute oral toxicity study was performed with reference to the test guidelines for acute oral toxicity test 425 [30] according to the Organisation for Economic Cooperation and Development. A limit dose of 2000 mg/kg body weight per oral was used. The signs of toxic effects and/or mortality were observed at 4 hours after administration, then for the next 48 h. The body weight was recorded for 14 consecutive days (OECD Guideline 2011) [31].

Induction of Skin Cancer in Mice: Skin carcinogenesis is a stepwise process consisting of initiation, promotion, and progression to induce skin tumors. The animals were divided into six

groups and the hairs were removed from the back of each mouse by the application of depilatory cream. They were kept in standard laboratory conditions for two days before the initiation of the experiment. Then 100 µL DMBA (100 µg/100 µL acetone) was applied on the dorsal side of the mice. After two weeks of initiation, tumor promotion was started by the topical application of 100 µL of 1% v/v of croton oil in acetone, three times a week [32], for 56 days. During the experimental period of eight weeks, all the animals were observed regularly on daily basis and body weight was observed on weekly basis. At the end of the experiment all were sacrificed and the selected parameters were evaluated [33].

Experimental Protocol:

- **Group-I, n=6:** This group served as a normal saline control group. All animals belonging to this group received a topical application of saline water on the dorsal surface of the skin (5 mL/kg body weight p.o.).
- **Group-II, n=6:** This group served as a negative control. All animals belonging to this group received a topical application of DMBA followed by croton oil twice a week as a promoter, after a week of DMBA application for two months on the dorsal surface of the skin.
- **Group-III, n=6:** This group served as positive control. All animals belonging to this group received a topical application of DMBA followed by croton oil twice a week as a promoter, after a week of DMBA application for two months on the dorsal surface of the skin. Treatment against DMBA induced tumor was provided by using standard drug (5-Fluorouracil) for two months.
- **Group-IV, n=6:** This group served test group I. All animals belonging to this group received a topical application of DMBA followed by croton oil twice a week as a promoter after a week of DMBA application for two months on the dorsal surface of the skin. Treatment against DMBA-induced tumor was provided by using a test drug *i.e* PTO 200mg/kg.p.o for two months.
- **Group-V, n=6:** This group served test group II. All animals belonging to this group received a topical application of DMBA followed by croton oil twice a week as a promoter after a week of DMBA application for two months on the dorsal surface of the skin. Treatment against DMBA induced tumor was provided by using a test drug *i.e* ETO 200mg/kg.p.o; for two months.
- **Group-VI, n=6:** This group served test group III. All animals in this group received a topical application of DMBA followed by croton oil twice a week as a promoter after a week of DMBA application for two months on the dorsal surface of the skin. Treatment against DMBA-induced tumor was provided by using a test drug, i.e., ATO 200mg/kg.p.o for two months.

Determination of Morphological Profile [34]:

Body Weight: The body weight of each mouse was measured from the first day to the last day of the experiment every week.

Tumor Incidence: The tumor incidence was measured on the last day of the study, which was considered as how many mice carry only a single tumor, which is expressed as a percentage incidence.

Tumor Burden: The tumor burden was estimated based on the average number of tumors per tumor-bearing mice at the last day of the study.

Tumor Yield: Tumor yield depends on the average number of tumors per mice and is calculated at the last day of study.

Tumor Diameter: The tumor diameter was measured by the diameter of tumors per mice at the last days of study.

Determination of Biochemical Profile:

Catalase: Catalase movement was estimated by the strategy utilized by Aebi (1984). A phosphate cushion (50mM) was utilized to prepare the homogenate, and the prepared homogenate was centrifuged at 4300 g for 10 min [35]. The change in absorbance was determined spectrophotometrically at a wavelength of 240 nm. The movement of the enzymes was expressed as U/mg of tissue, where U is mmol of hydrogen peroxide vanishing/min [36].

Reduced Glutathione (GSH): The level of GSH was estimated as total non-protein sulfhydryl group

by the method developed by the Moron et al. Free endogenous-SH was assayed and the absorbance was recorded at 412 nm [37] using an UV-Visible spectrophotometer. Reduced GSH was used as a standard and the levels of GSH were expressed as mmol/g of tissue.

Superoxide Dismutase (SOD): Superoxide dismutase (SOD) level was estimated by the evaluation of pyrogallol auto-oxidation hindrance, and the outcomes were communicated as units/mg protein. Auto-oxidation of pyrogallol in Tris (hydroxymethyl) aminomethane (THAM) hydrochloride buffer was estimated by measuring absorbance at 420 nm [38, 39].

Lipid Peroxidation (LPO): The LPO level was determined spectrophotometrically using the thiobarbituric acid reactive substances method, as described by Ohkhawa et al. The optical density of LPO was measured at 532 nm, and the content of thiobarbituric acid reactive substances was expressed as nmol/mg of tissue [40].

Total Protein: The total protein content of the tumor was assessed by the method described by Lowry *et al.* Homogenate was prepared in distilled water, and absorbance was recorded at 670 nm. Protein concentration was estimated from a standard curve of ox-like serum albumin, and the level was expressed as mg/g [41, 42].

Statistical Analysis: All values were expressed as the mean ± SEM. The analysis was performed by using a Graph pad prism. The data were subjected to ANOVA followed by Dunnett's test, and $P < 0.05$ was considered statistically significant.

RESULTS:

Toxicity Studies: Since, the extracts were found safe up to the dose level of 2000 mg/kg body weight hence, 1/10th dose (200 mg/kg body weight) of different extracts was selected for evaluating the effect against DMBA-induced skin cancer in mice.

Morphological Studies:

Body Weight: Each mouse's body weight was measured weekly. The value is presented in the initial and final days of the study. The body weight was gradually elevated in the normal group. However, the control group gradually declined in body weight throughout the study compared to the normal group. All the treatment groups showed a significant recovery in body weight compared to the control group. All the results are shown in **Table 1.**

Tumor Incidence: The tumor incidence was significantly ($P<0.001$) increased in group II compared with the group-I group.

The tumor incidence was significantly ($P<0.001$) reduced in all treated groups compared to the control group. Group III and group- (test group II) at dose of 200mg/kg showed a higher reduction in tumor incidence than Group -IV and Group –VI. All results are shown in **Table 1** and **Fig. 1.**

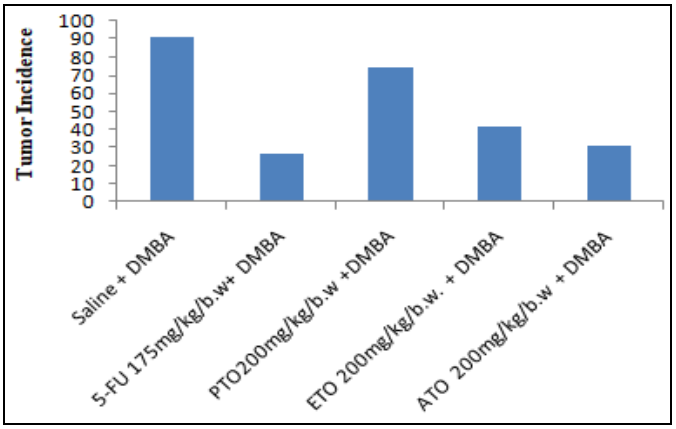

FIG. 1: RESULTS OF TUMOR INCIDENCE OF DIFFERENT EXPERIMENTAL GROUPS

Tumor Burden: The tumor burden was significantly ($P<0.001$) elevated in group II compared to the normal group. All the treatment groups significantly reduction in the tumor burden.

The tumor burden was significantly ($P<0.001$) removed in group III and group V (test group II) as compared with group II. Treatments group-IV and VI were found to be less effective than that of group V as shown in **Table 1** and **Fig. 2.**

Tumor Yield: The tumor yield was significantly ($P<0.001$) increased in group II compared with group-I. The tumor yield was significantly ($P<0.001$) reduced in all treated groups compared to group II. The group-III and group-V (test group II) at a dose of 200 mg/kg showed highly reduction in tumor yield.

The group-IV and Group-VI groups reduced the tumor yield but less effective. All results are shown in **Table 1** and **Fig. 2.**

TABLE 1: EFFECT OF LEAVES EXTRACTS OF *T. OFFICINALE* LAM. ON MORPHOLOGICAL PROFILE ON DMBA-INDUCED SKIN CARCINOGENESIS IN SWISS ALBINO MICE

Treatment Groups Dose /mg/kg	Body Weight (g)		Tumor Incidence	Tumor yield	Tumor diameter	Tumor Burden
	Initial	Final				
Group-I 2ml Saline/kg/b.w. p.o.	31.83±1.54	36.18± 1.75	00	00	00	00
Group-II 2ml Saline/kg/b.w. p.o. + DMBA	34.17±0.97	28.81± 1.90	91.34 ±1.67***	7.8 ± 0.98***	1.86±0.092***	7.8 ± 0.54**
Group-III 5-Fluorouracil 175mg/kg/b.w. p.o. + DMBA	34.33±1.13	37.58 ± 1.15	27.15±0.56**	3.97± 0.13***	1.14±0.041***	3.87 ± 0.22*
Group-IV PTO 200mg/kg/b.w.p.o. + DMBA	30.67±0.35	32.83 ± 1.09	75.15±0.66**	5.95 ± 0.87***	1.54±0.10***	5.85 ± 0.36*
Group-V ETO 200mg/kg/b.w.p.o. + DMBA	31.50±0.13	34.33 ± 1.14	31.62±0.53**	4.03± 0.36***	1.27±0.24***	4.20 ± 0.58*
Group-VI ATO 200mg/kg/b.w.p.o. + DMBA	32.67±1.35	33.64 ± 1.56	57.92±1.44**	6.85± 0.14**	1.61±1.09**	6.99± 1.03*

The values are expressed as mean ± SEM for six animals in each group. The group-II is compared with group-I. The drug treated groups were compared with Group II. The P value less than ***P<0.001,**P<0.01, and *P<0.05 is considered as significant.

Tumor Diameter: The tumor diameter significantly (P<0.001) increased in Group II when compared with group-I. However, the tumor diameter was significantly (P<0.001) decreased in all treatment groups. However, group IV and group -VI were less effective than group-III and V. All results are shown in **Table 1** and **Fig. 2.**

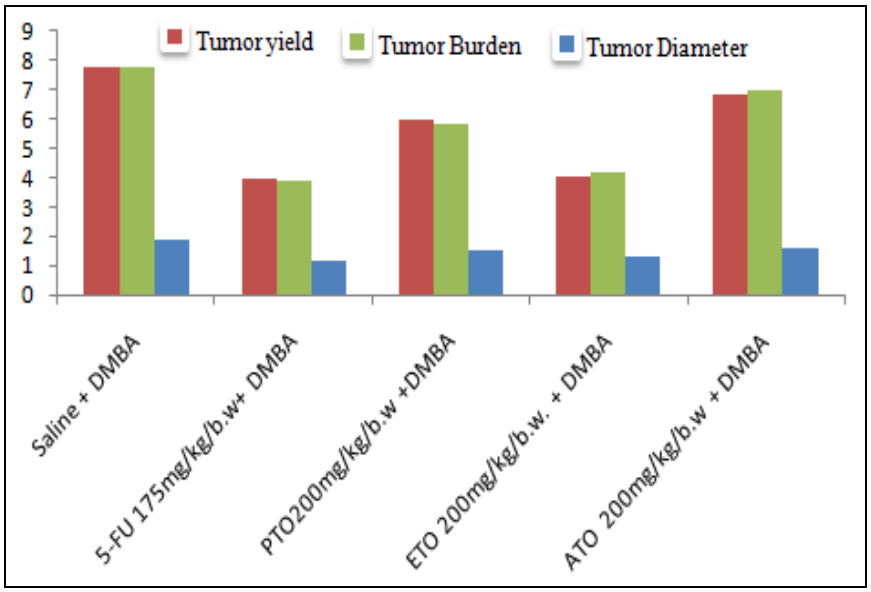

FIG. 2: RESULTS OF TUMOR YIELD, TUMOR BURDEN, AND TUMOR DIAMETER OF DIFFERENT EXPERIMENTAL GROUPS

Determination of Biochemical Profile:

Catalase: The level of catalase enzyme was significantly (P<0.001) decreased in the serum of DMBA-induced skin tumor in group II when compared with group-I.

Treatment group III and group V showed significantly (P<0.001) increased catalase enzyme levels compared to the control group.

The group-IV (P<0.01) and group VI (P<0.05) were found to be less significant, as shown in **Fig. 3** and **Table 2.**

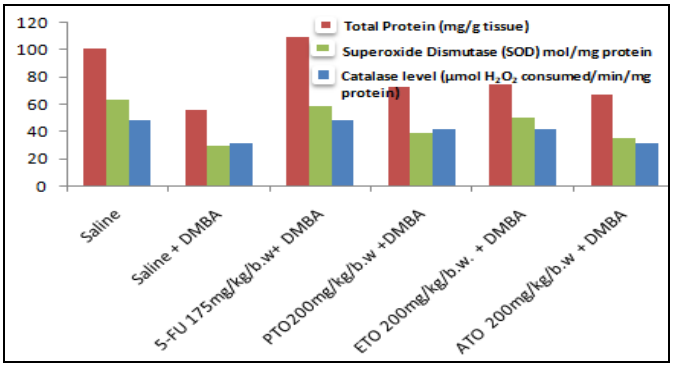

FIG. 3: RESULTS OF TOTAL PROTEIN, SUPEROXIDE DISMUTASE, AND CATALASE LEVELS OF DIFFERENT EXPERIMENTAL GROUPS

TABLE 2: EFFECT OF LEAVES EXTRACTS OF *T. OFFICINALE* LAM. ON BIOCHEMICAL PROFILE ON DMBA-INDUCED SKIN CARCINOGENESIS IN SWISS ALBINO MICE

Treatment Groups Dose/mg/kg	Catalase level (µmol H_2O_2 consumed/min/mg protein)	Reduced Glutathione (µmol/mg tissue)	Superoxide Dismutase (SOD) mol/mg protein	Lipid Peroxidation (nmol/mg tissue)	Total protein (mg/g tissue)
Group-I 2ml Saline/kg/b.w. p.o.	48.52 ± 7.97	7.16 ± 1.35	63.15 ± 13.06	4.85 ± 0.91	100.54 ± 16.84
Group-II 2ml Saline/kg/b.w. p.o. + DMBA	32 ± 2.56***	2.85 ± 1.61***	29.7 ± 9.54***	12.4 ±1.72***	55.91 ± 8.97***
Group-III 5-Fluorouracil- 175mg/kg/b.w. p.o. + DMBA	47.94 ± 8.24***	6.45 ± 0.85***	58.97 ± 8.56***	7.8 ± 1.65***	109.12 ± 15.7***
Group-IV PTO 200mg/kg/b.w.p.o. + DMBA	36.74 ± 4.52**	4.78 ± 0.94**	38.76 ± 5.85[b]**	10.76 ±1.19**	72.89 ± 14.82**
Group-V ETO 200mg/kg/b.w.p.o. + DMBA	41.55 ± 62 ***	5.35 ±0.86***	49.83 ± 11.25***	9.86 ± 1.72***	74.77 ± 15.64***
Group-VI ATO 200mg/kg/b.w.p.o. + DMBA	31.59 ± 3.67*	3.53 ± 0.74*	35.71 ± 5.29*	11.55 ± 1.44*	67.23 ± 12.89*

Reduced Glutathione (GSH): The GSH level was significant (P<0.001) reduced in group II when compared with group-I. The group-II and group V observed significant (P<0.001) recovery in the level of GSH enzyme as compared to Group IV (P<0.01) and VI (P<0.05) when compared with group II, as shown in **Fig. 4** and **Table 2.**

Superoxide Dismutase (SOD): The superoxide dismutase level significantly (P<0.001) declined in group II compared with group-I. Treatment groups III and V showed significant (P<0.001) recovery in the level of SOD. However, Group IV (P<0.01) and group-VI(P<0.001) showed less significant recovery in the SOD level as compared with group-II as shown in **Fig. 3** and **Table 2.**

Lipid Peroxidation (LPO): The LPO level showed a significant increase (P<0.001) in group II compared with group-I. All the treatment groups significantly recovered the level of LPO enzyme. The LPO level significantly declined (P<0.001) in group III and V compared with the control group. Group IV (P<0.01) and group-VI (P<0.05) showed less significance in restoring the LPO level, as shown in **Fig. 4** and **Table 2.**

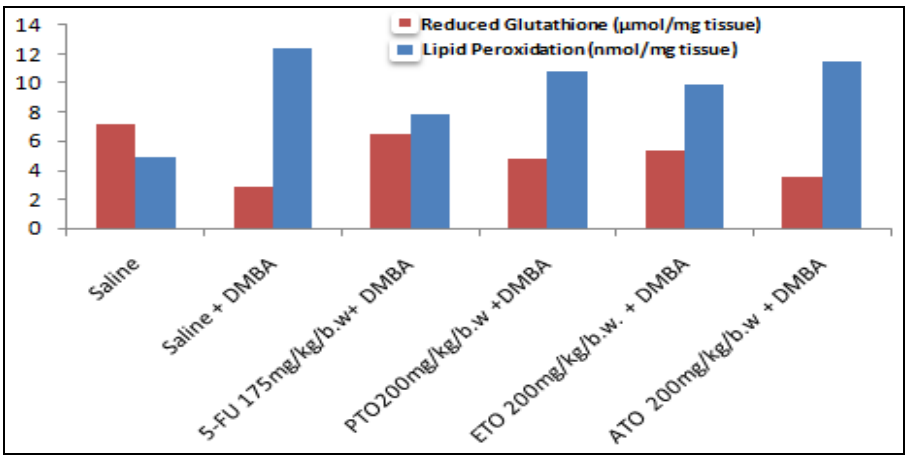

FIG. 4: RESULTS OF REDUCED GLUTATHIONE AND LIPID PEROXIDATION LEVELS OF DIFFERENT EXPERIMENTAL GROUPS

Total Protein: Total protein content was significantly (P<0.001) decreased in group II compared with group-I. All treatment groups significantly improved the level of total protein content compared with group-I. The group-III and group V showed significant (P<0.001) improvement in the level of total protein; however, group-IV and VI groups were found to be less significant (P<0.01) (P<0.05) when compared with group-II as shown in **Fig. 3** and **Table 2.**

CONCLUSION: Present study aimed to evaluate the chemopreventive nature of different extracts (PTO, ETO, and ATO) of *T. officinale* Lam. leaves on DMBA-induced skin cancer in swiss albino mice. The result of our study revealed the antiproliferative effect of three different extracts by restoring the normal composition of the skin tissues. All the extracts were evaluated at a dose of 200mg/kg.p.o for various biochemical parameters such as catalase, reduced glutathione, superoxide dismutase, lipid peroxidation level, and total protein using 5-fluorouracil as a standard drug. The ETO extract showed a comparative effect with standard drug, *i.e.*, 5-fluorouracil, among all three. Thus, from the above-mentioned results, it could be inferred that the leaves of *T. officinale* Lam could be a better option and alternative against allopathic chemotherapeutic agents. The plant can further be evaluated for *in-vivo* studies using cell lines.

Consent for Publication: Not applicable.

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CONFLICTS OF INTEREST: None

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