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CHEMOPREVENTIVE POTENTIAL OF *CAPPARIS DECIDUA* FRUIT EXTRACT AGAINST DMBA INDUCED SKIN CARCINOGENESIS IN SWISS ALBINO MICE

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ABSTRACT: Chemoprevention is the novel approach that inhibits and delays or reverses the process of cancer development by using natural herbs and plant products. The aim of the present study was to evaluate the anticancer efficacy of orally administered *Capparis decidua* fruit extract (CDE) on skin carcinogenesis model in swiss albino mice by the single topical application of the 7,12 dimethylbenz (a)anthracene (100µg/100µl of acetone) followed by croton oil after 2 weeks (1% in acetone/thrice in a week). Oral administration of the CDE at a dose of 50 mg/kg b.wt./day during the peri initiation stage (one week before DMBA and one week after the application followed by croton oil till the end of the experiment) and post-initiation stage (after 2 weeks DMBA application, from the day of croton oil treatment till the end of the experiment). A significant reduction in the tumor incidence, tumor burden, and a cumulative number of papillomas was observed, along with the increase in the average latent period in mice treated with CDE drugs compared with DMBA/croton oil-treated group III. A significant elevation was seen in the level of the non-enzymatic antioxidant reduced glutathione (GSH), antioxidant enzymes catalase and superoxide dismutase with a reduction in lipid peroxidation (LPO) in the liver and skin of the mice in both the above-mentioned groups in comparison to DMBA+ croton oil-treated group. The results clearly indicate that the CDE has potent chemopreventive efficacy against two-stage skin carcinogenesis, which can be attributed to its antioxidative and antiperoxidative effects.

INTRODUCTION: Cancer is one of the most important causes of death in the population after cardiovascular diseases. It is the second leading cause of death in developed countries. Cancer is not a single disease but is a group of many different diseases that all share biological and pathological characteristics.

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According to the World Cancer Report (2014), developed by the International Agency for Research on Cancer (IARC), predicts an activity of new cancer cases from an annual estimation of 14 million in 2012 to 22 million within 2 decades. It is expected that over the same period, cancer deaths will also increase from 8.2 million to 13 million per year [1, 2]. Incidences of skin cancer are increasing at a high rate. One of the reasons of skin carcinogenesis growth in the developed countries is due to the depletion of the ozone layer and changes in environmental composition drastically. The major incidence of skin cancer is present in Australia and European countries.

It is regarded as a dreaded disease there [3, 4]. Although UV radiation is the leading cause of skin cancer, exposures to various xenobiotic chemicals, biological agents, pesticides, pollutants, smoke also contribute to cancer incidence of cutaneous neoplasia in humans [5, 6]. Cancer chemoprevention is a significant promise to control the process of skin carcinogenesis. The potential uses of natural and synthetic agents have reduced cancer incidence and mortality in recent years. The use of the medicinal plants in dietary food has important effects as chemopreventive agent cancer models in animals [7, 8].

Humans have evolved antioxidant systems to protect against free radicals. These systems include some antioxidants produced in the body (endogenous antioxidants) and others obtained from the diet such as vegetables, fruits, *etc*. (exogenous antioxidants). The use of natural products that are present in the common diet and beverages normally consumed by all the human population has gained considerable attention. These products have shown to possess the chemopreventive potential in various cancers, including the skin. The plants are rich sources of antioxidants like polyphenols, flavonoids, flavanones, alkaloids, *etc*. which are known to possess anticancerous activity [6, 9].

C. decidua (Forssk.) Edgew. plant is a xerophytic plant. In this context, *C. decidua* has been selected for the present study rich in chemical compounds like alkaloids, flavonoids, phenolic compounds, terpenoids, steroids, vitamins, quaternary ammonium compounds, and many more phyto-constituents that are responsible for its medicinal value. The different plant parts have shown to exhibit a wide range of biological activities, including antimicrobial, antifungal, anti-inflammatory, hepatoprotective, antihelmintic, antidiabetic, antisebum, antihyperlipidemic, antisclerotic, antitermite, antiplaque, analgesic, sedative, and anticonvulsant [10, 11, 12, 13].

Due to the presence of sources of antioxidants it has medicinal value. However, the effect of *C. decidua* fruit extract (CDE) against skin carcinogenesis has not been studied. Hence, the present investigation has been undertaken to explore the effect of oral administration of CDE against DMBA and croton oil mediated two- stage skin carcinogenesis in terms of tumor development.

MATERIALS AND METHODS: Swiss albino mice (6-8 weeks old) weighing 24 ± 2gm were selected from inbred colony for the experiment. Animal experimental and handling were performed According to the guidelines of CPCSEA, and the Institutional Animal Ethics Committee (Reg. No. 1698/90/Re/S/12/CPCSEA) was approved the study. These animals were maintained in the animal house at a temperature of 25 ± 3° and 14 h light & 10 h dark period. The animals were housed in polypropylene cages. They were fed on standard mice feed obtained from Aashirwad Industries, Chandigarh and water was provided *ad libitum*.

Chemicals: 7, 12-Dimethyl Benz (a) anthracene (DMBA) and croton oil were procured from Sigma Chemical Co. (St. Louis, MO, USA). DMBA was dissolved at a concentration of 100 µg/100µl in acetone. Croton oil was mixed in acetone to give a solution of 1% dilution.

Plant Material and Extract Preparation: Fruits of *Capparis decidua* L. were collected locally after their proper identification by a competent botanist (Voucher Specimen No: RUBL-211371) from the herbarium, Department of Botany, University of Rajasthan, Jaipur. The whole fruits were shade dried and powdered.

The hydro-alcoholic extract was prepared by refluxing with double-distilled water (DDW) and ethanol (3:1) for 36 (12 × 3) hrs at 40 ºC. The extract was cooled and concentrated by evaporating its liquid contents. The prepared *C. decidua* extract (CDE) was stored at a low temperature until further use. The extract was re-dissolved in DDW prior to the oral administration in mice.

Optimum Dose Selection: Different doses of CDE 5, 10, 25, 50, 100, 150 mg/kg body weight/day for 15 consecutive days were given orally. The morphological and behavioral changes were recorded for 30 days. The biochemical changes in the level of lipid peroxidation (LPO) and glutathione (GSH), and total proteins in the liver were estimated after an autopsy on day 16th and 30th post-treatment. The dose showing the highest levels of GSH and total protein, and the lowest

level of LPO was selected to carry out further experiments. The selected dose of 50 mg/kgb.wt./ mice was prepared for treatment by dissolving the extract in double-distilled water.

Experimental Design: To test the chemo-preventive efficacy of CDE against DMBA and croton oil-induced mouse skin papillomagenesis, fifty mice were divided equally into five groups of 10 mice each. The dorsal skin of the mice was shaved two days before the commencement of the experiment, and only those animals in the resting phase of the hair cycle were chosen for the study.

For induction of tumors, a two-stage protocol consisting of initiation with a single topical application of a carcinogen (7, 12 - dimethylbenz (a) anthracene (DMBA) followed by a promoter (croton oil) three times a week.

Group I: Control (Vehicle Only): Mice of this group received only the topical application of acetone (100µl/mouse) on the shaved dorsal skin for 16 weeks and was considered as a negative control group.

Group II: CDE Treated: Mice of this group were administered an optimum dose of CDE (50 mg/kg/ b.wt./day/animal) by oral gavage once a day during the entire experimental period of 16 weeks.

Group III: DMBA + Croton oil: Mice of this group were applied with a single topical application of DMBA (100µg/100µl of acetone) over the shaved area of the skin. Two weeks later, after the initiation, croton oil (1% v/v in acetone) was applied three times a week until the end of the experiment (16 weeks).

Group IV: CDE+DMBA + Croton oil (Peri-initiation): Mice of this group were treated with daily oral administration of CDE (50 mg/kg/b.wt./ day/animal) for 7 days prior to the DMBA application and 7 days post application. Croton oil was also administrated topically to these animals three times a week until the end of the experiment (16 weeks).

Group V: DMBA + Croton oil + CDE (Post-initiation): Mice of this group were administrated CDE (50 mg/kg/b.wt./day/ animal) orally after the two weeks of DMBA application, from the first day of croton oil topical application, and continued till the end of the experiment (*i.e.* 16 weeks).

Morphological Analysis of Tumors: The chemopreventive response was assessed on the basis of the cumulative number of papillomas, tumor incidence, burden, yield, and average latent period and were calculated as follows:

Cumulative Number of Papillomas: Total number of tumor-bearing mice by the end of the experiment were recorded.

Tumor Incidence: The number of mice carrying at least one tumor expressed as percent incidence.

Tumor Burden: The average number of tumors per tumor-bearing mice.

Tumor Yield: The average number of papillomas per mouse.

Average Latent Period: The average latent period was calculated by multiplying the number of tumors appearing each week by the time in weeks after the application of the promoting agent and dividing the sum by the total number of tumors.

$$\text{Average latent period} = fx/n$$

Where f is the number of tumors appearing in each week, x is the number of weeks and n is the total number of tumors.

Tumor Diameter: The diameter of each tumor was measured during the experiment.

Tumor Weight: The weight of each tumor in animals at the termination of each experiment was measured.

Biochemical Study: After the completion of the experiment, *i.e.,* 16 weeks, the mice were sacrificed by cervical dislocation. The biochemical alterations were estimated in the liver and skin of mice.

Estimation of Reduced Glutathione (GSH) Level: Reduced glutathione (GSH) in liver and skin were determined by the method as described by [14] and expressed as µ mole GSH/gm tissue. Homogenate was prepared by mixing 1 gm of liver or skin tissue with 9 ml 1.15% KCl solution (10% weight/volume) and then centrifuged for 10 min at 2500 rpm. 500 µl supernatant was taken out, and

100 µl of 25% TCA was added, thereafter again centrifuged for 10 minutes. 100 µl of this supernatant (sample) was added to 900 µl of 0.2 M NaP (pH 8.0), and 2 ml of 0.6 M DTNB (forming a complex with –SH group) were added. In blank, 100 µl 25% TCA was added to 900 µl of 0.2 M NaP (pH 8.0) and 2 ml of 0.6 M DTNB. The absorbance of the sample was read against the blank at 412 nm using a UV-VIS Systronics Spectrophotometer.

Determination of Lipid Peroxidation (LPO): Lipid peroxidation level was estimated spectro-photometrically by the thiobarbituric acid reactive substances (TBARS) method given by [15]. The content of the TBARS was expressed as nmoles of malondialdehyde/mg of tissue using 1,1,3,3,-tetra methoxy-propane (TMP) as standard. Homogenate was prepared by mixing 1 gm of liver and skin with 9 ml 1.15% KCl solution (10% weight/volume). Took 0.8 ml of sample in a test tube and added 0.2 ml of 8.1% sodium dodecyl sulphate (SDS) + 1.5 ml of 20% acetic acid, and the pH adjusted to 3.5 with NaOH. 1.5 ml of 0.6 % aqueous solution of thiobarbituric acid (TBA) was added. The mixture was heated at 95 °C for 1 h than after cooling in tap water, 5 ml of n-butanol: pyridine (15: 1 v/v) were added and shaken vigorously. The solution was centrifuged at 4000 rpm for 10 min. The organic layer was taken and its absorbance was read at 532 nm using a UV-VIS Systronics Spectrophotometer.

Determination of the Superoxide Dismutase Activity: The antioxidative enzyme activities of superoxide dismutase (SOD) in liver and skin homogenate were determined by the method of [16]. The results were expressed as U/mg of tissue, where U is the unit of enzyme activity defined as the amount of enzyme necessary for inhibiting the 50% autooxidation of pyrogallol. The liver/skin was trimmed and cut into small pieces and was then weighed 0.5 gm. Homogenate was prepared in 5 ml of DDW, *i.e.*, double distilled water. Now in cuvette, 1.5 ml of 100 mM Tris – HCl buffer, 0.5 ml of 6 mM EDTA, 5µl tissue homogenate, and 1 ml of 0.6 mM pyrogallol solution were added. The rate of auto-oxidation of pyrogallol was taken from the increase in absorbance at 420 nm in a spectrophotometer.

Determination of the Catalase Activity: The activity of catalase (CAT) in liver and skin homogenate were determined according to the method described by [17]. The activity of the enzyme was expressed as U/mg of tissue, where U is µ mole of H_2O_2 reduced/min/mg tissue. The liver and skin were trimmed and cut into small pieces and were then weighed 0.5 gm.

Homogenate was prepared in 5 ml of phosphate buffer, and cold centrifuged for 10 min at 6000 rpm. 1 ml of phosphate buffer, 0.1ml of tissue homogenate, and 0.4 ml of 30 mM H_2O_2 were also added in the cuvette. A decrease in absorbance at every 10-sec interval for 30 sec at 240 nm in a UV spectrophotometer was recorded.

Statistical Analysis: One-way ANOVA followed by post hoc test Tukey's test was performed. $p < 0.05$ was considered as significant for the experiment. The values are expressed as mean ± SEM.

RESULTS:

Morphological study: Table 1 and **2** indicates the chemopreventive effect of CDE on DMBA initiated and croton oil in two stages skin carcinogenesis. There was no apparent acute toxicity of CDE observed in the body weights or after gross morphological examination of major organ systems. In group III animals (DMBA + croton oil) papillomas started appearing from eight weeks onwards, and 100% incidences were reached by the time of termination of the experiments (*i.e.*, 16 weeks). The cumulative number of papillomas in these mice were 68. The average number of papillomas per mouse (tumor yield) was found to be 4.16 ± 0.79 **Table 2**, while the average tumor weight was 2.57 gm **Table 1**.

Mice of group IV and V, which were given the continuous treatment of CDE orally at peri initiation phase (*i.e.*, one week before DMBA application and a week after DMBA application) and post-initiation group (*i.e.*, 2 weeks prior DMBA application until the end of 16 weeks) showed a significant reduction in incidence of the tumor by 20% and 40% respectively in comparison to the group III **Table 2**. At the termination of the experiment at 16 weeks, 68 tumors were recorded in animals of group III, whereas only 46 and 27 tumors were recorded in CDE treated groups IV and V, respectively.

In group III (DMBA + croton oil) the tumors appeared in the 8th week, whereas in group IV and V they appeared by 10 and 11 weeks *i.e.* the appearance was delayed by 2 and 3 weeks respectively in group IV and V where CDE was supplemented to mice. Tumor yield observed in group III was significantly lower in group IV and V, respectively. It was 3.47 and 2.64 only in comparison to 4.16 observed in group III **Table 2**. Furthermore, supplementation of CDE also resulted in a significant decrease in tumor size and tumor weight comparison to Group III. Tumor weight in the CDE treated group IV, and V was 1.89 and 1.254gm, respectively **Table 1**. CDE also prolonged the average latency period (*i.e.*, time lag between the application of the promoter and the appearance 50% tumor) of tumors by approximately 3.02 and 3.48 weeks in groups IV and V, respectively compared to group III mice **Table 2**. No tumors developed in mice of group I and Group II.

TABLE 1: TUMOR SIZE AND WEIGHT IN DMBA INDUCED AND CROTON OIL PROMOTED SKIN CARCINOGENESIS IN SWISS ALBINO MICE WITH OR WITHOUT CDE TREATMENT

Groups	Tumor diameter (mm)		Tumor weight
	2-5mm	6-9 mm	(gm)
Group I: Control (Vehicle only)	-	-	-
Group II: CDE treated	-	-	-
Group III: DMBA + croton oil	51	17	2.57
Group IV: CDE+ DMBA + croton oil (Peri-initiation)	33	13	1.89
Group V: DMBA + croton oil + CDE (Post-initiation)	15	12	1.254

TABLE 2: CHEMOPREVENTIVE EFFECT OF CDE ON DMBA INITIATED AND CROTON OIL PROMOTED SKIN CARCINOGENESIS IN SWISS ALBINO MICE WITH OR WITHOUT CDE TREATMENT

Groups	Cumulative number of tumors	Tumor incidence	Tumor burden	Tumor yield	Average latent period (weeks)
Group I	-	-	-	-	-
Group II	-	-	-	-	-
Group III	68	100%	4.39 ±0.704	4.16 ± 0.79	10.51
Group IV	46	80%	3.47 ± 0.629	2.64 ± 0.56	11.02
Group V	27	60%	2.64 ± 0.502	1.56 ± 0.31	11.48

Data are presented as mean ± SEM in tumor burden and tumor yield.

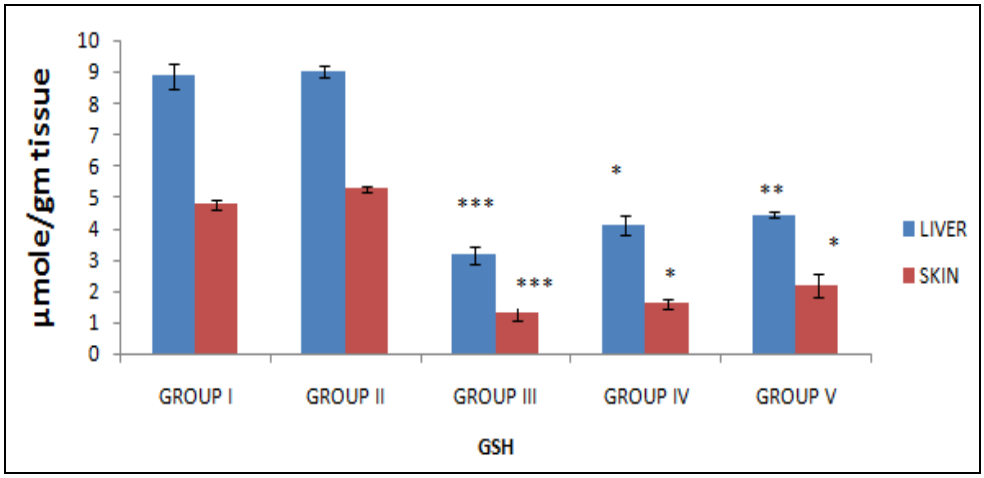

FIG. 1: VARIATION IN THE REDUCED GLUTATHIONE (GSH) DURING DMBA INDUCED SKIN CARCINOGENESIS WITH OR WITHOUT CDE ADMINISTRATION. Data are presented as mean ± SEM; Statistical comparison: control (vehicle only) v/s DMBA + croton oil; DMBA + croton oil v/s peri-initiation and post-initiation groups; Significance levels: ***p≤ 0.001, **p≤ 0.01, *p≤ 0.05

Biochemical Studies: In the present experiment, there was no significant elevation observed in the GSH, LPO, catalase, and SOD in the liver and skin of mice of group II which received CDE alone for 16 weeks when comparison to the vehicle-treated control (group I). Significant ($p<0.001$) decrease in the level of GSH, SOD, and catalase and the significant increase in the LPO level in both liver and skin tissues in DMBA+ croton oil-treated (group III) in comparison to the group I was noted. The GSH level in the liver was found to be significantly increased ($p<0.05$) at peri and (p 0.01) post-initiation group (IV and V), respectively, in comparison to the group III. A significant elevation

(p<0.05) of GSH in the skin was also found to be in post-initiation (group V), in comparison to group III **Fig. 1**. Significant (p<0.001) increase in the LPO level was estimated in both liver, and skin tissues in DMBA+ croton oil-treated (group III) in comparison to the group I. Increased LPO (p<0.001) in carcinogen-treated group III was significantly reduced (p<0.001, p<0.05) in liver and skin, respectively in both the group's IV and V **Fig. 2**.

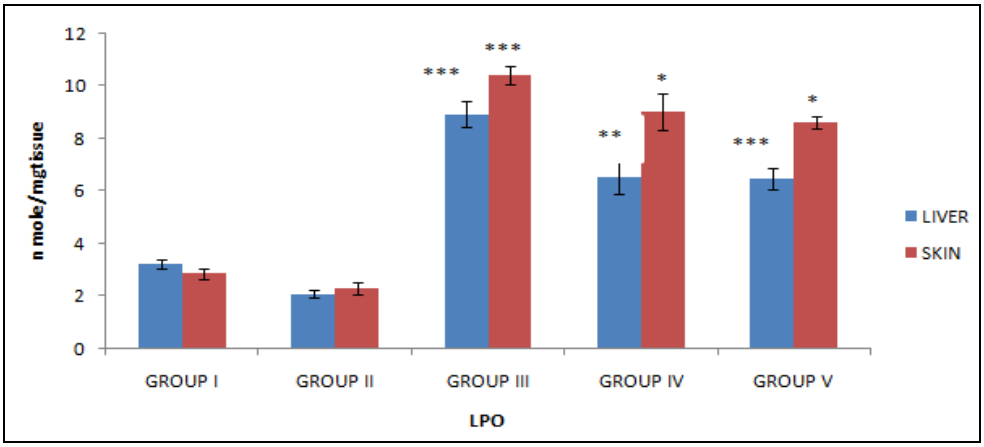

FIG. 2: VARIATION IN THE LIPID PEROXIDATION (LPO) DURING DMBA INDUCED SKIN CARCINOGENESIS WITH OR WITHOUT CDE ADMINISTRATION. Data are presented as mean ± SEM; Statistical comparison: control (vehicle only) v/s DMBA + croton oil; DMBA + croton oil v/s peri-initiation and post-initiation groups; Significance levels: ***p≤ 0.001, **p≤ 0.01, *p≤ 0.05

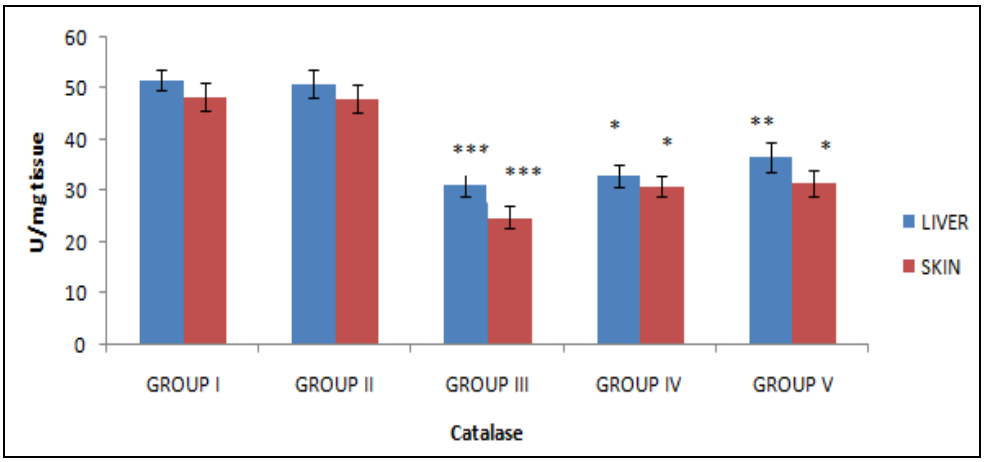

FIG. 3: VARIATION IN THE CATALASE ACTIVITY DURING DMBA INDUCED SKIN CARCINOGENESIS WITH OR WITHOUT CDE ADMINISTRATION. Data are presented as mean ± SEM; Statistical comparison: control (vehicle only) v/s DMBA + croton oil; DMBA + croton oil v/s peri-initiation and post-initiation groups; Significance levels: ***p≤ 0.001, **p≤ 0.01, *p≤ 0.05

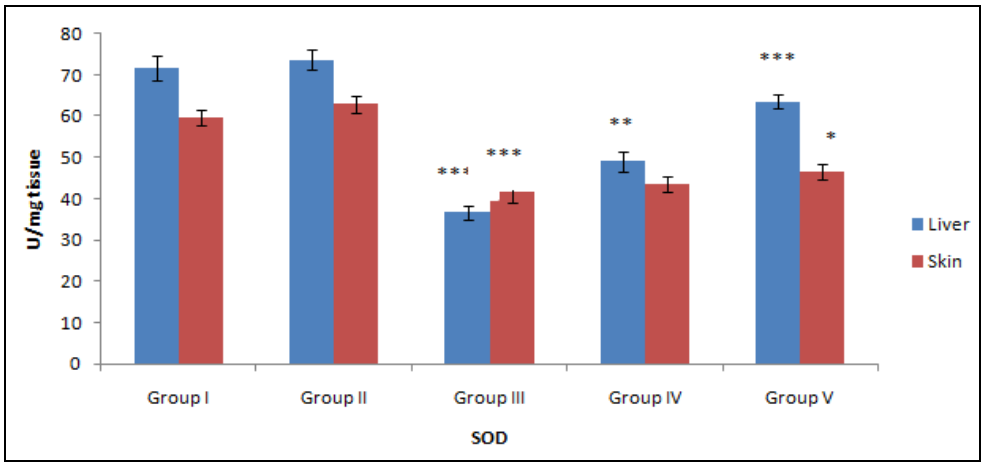

FIG. 4: VARIATION IN THE SUPER OXIDE DISMUTASE (SOD) DURING DMBA INDUCED SKIN CARCINOGENESIS WITH OR WITHOUT CDE ADMINISTRATION. Data are presented as mean ± SEM; Statistical comparison: control (vehicle only) v/s DMBA + croton oil; DMBA + croton oil v/s peri-initiation and post-initiation groups; Significance levels: ***p≤ 0.001, **p≤ 0.01, *p≤ 0.5

In group III (DMBA + croton oil) catalase activity estimated was significantly ($p<0.001$) depleted, which was significantly elevated in group IV and V, respectively, where CDE was supplemented **Fig. 3**. The level of SOD significantly ($p<0.001$) decreased in both liver and skin tissues in DMBA+ croton oil-treated (group III) in comparison to the group I, which could be significantly enhanced in the liver of group IV and V ($p<0.01$) and ($p<0.001$) respectively. In contrast, the skin mice of group IV showed no significant elevation in the SOD levels **Fig. 4**.

The results indicate that the administration of CDE in group V is more effective, as evidenced by the results obtained as it could restore them to nearly normal levels.

DISCUSSION: The present study has clearly shown that the oral administration of CDE exerts a strong chemopreventive effect against DMBA-initiated + croton oil promoted two-stage skin carcinogenesis in Swiss albino mice. It is clearly evidenced that tumor incidence was reduced significantly along with tumor burden and tumor yield. CDE treatment also resulted in a significantly lower cumulative number of papilloma's and longer tumor latent periods.

The chemically induced two-stage skin carcinogenesis in the mouse model is particularly useful to examine the genetic and biochemical changes. Chemical carcinogens such as DMBA can bind to DNA and result in mutagenic events that contribute to malignancy [18, 19]. The pro-carcinogenic nature of DMBA is metabolized by phase I enzymes such as cytochrome P450 to 3,4-diol-1,2-epoxide, its ultimate carcinogenic metabolite, which covalently binds to DNA and form DNA adducts which cause mutation and carcinogenesis [20]. Oxidative stress caused by Reactive Oxygen Species (ROS) which are generated excessively during the metabolic activation of DMBA, contributes to the pathogenesis of cancer [21, 22, 23].

It was reported that chemical carcinogenesis was inhibited by the blocking agents that could exert their preventive effect by several mechanisms, which included enhancing the detoxification of carcinogens, inhibiting cytochrome P450-mediated activation of carcinogens, scavenging free radicals, and preventing their interaction with DNA [24, 25].

The consumption of crude extract of CDE showed significant improvement in all the biochemical parameters by restoring them to normal levels. The present study reported a significant enhancement in the activities of non-enzymatic as well as enzymatic antioxidants in the liver and skin of mice. The DMBA + Croton oil (group III) was deprived of antioxidants such as GSH, SOD, and catalase because they are consumed during the oxidative stress, but the CDE administration in Group IV and V normalized the antioxidant content of the cells. GSH is an important non-proteinthiol antioxidant that plays a significant role in protecting cells against oxidative stress and is used to scavenge free radicals generated during carcinogen metabolism. This results in the inhibition of skin carcinogenesis [26]. In the present study, the elevated levels of GSH induced by CDE in group IV and V in the mice skin and liver probably helped in the elimination of free radicals.

SOD is a metalloprotein and chain-breaking antioxidant that converts superoxide radicals into hydrogen peroxide, inhibiting the generation of reactive oxygen species cascade, and catalase breaks down H_2O_2 into water and oxygen [27, 28]. The enhancement in the SOD and catalase level during the current study demonstrates the antioxidative potential of CDE. The dose of antioxidants in the form of CDE helped to restore the levels in Group IV and V. Treatment prior to the DMBA application might prevent cancer, but it was more effective when continued till the end of the experiment.

DMBA generated free radicals lead to the deterioration of membranes and proteins by the lipid peroxidation reaction. LPO is increased during the carcinogenic process, and malondialdehyde (MDA) as secondary metabolites was observed to be the most mutagenic and carcinogenic product of the reaction [29, 30]. In the present study, the level of increased malondialdehyde in Group III was found to be significantly reduced by supplementation of CDE in peri and post-initiation groups.

The antioxidant and anti-inflammatory activity was previously evaluated in *C. decidua* seed. It is a rich

source of β-sitosterol, which exerted statistically significant and dose-dependent anti-inflammatory activity in carrageenan-induced rat paw edema. The topical application of β-sitosterol significantly inhibited ear inflammation induced by tetradecanoylphorbol-13-acetate (TPA) in mice [12, 31].

Fruit powder of *C. decidua* reduced alloxan-induced lipid peroxidation and subsequently altered superoxide dismutase and catalase in erythrocytes, kidney, and heart tissues. It reduced oxidative stress in diabetes [12, 29, 32]. The anticancerous efficacy of C. *decidua* has not been explored so far. The results obtained from the present findings clearly suggest the cancer-preventive potential and antioxidant property of CDE against DMBA-initiated and croton oil-promoted skin tumorigenesis in the Swiss albino mice.

CONCLUSION: In conclusion, the results of the present investigation suggest that the *C. deciduas* fruit considered as a dietary agent exhibits potent anticancer and antioxidative activities. These facts indicate the scientific basis of *C. decidua* being used as traditional medicine. However, further experiments are needed to determine the pharmaceutical potential of the plant as preventive medicine against cancer in the human population.

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CONFLICTS OF INTEREST: There are no conflicts of interest among the authors.

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