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Research Article

The Effect on Skin Papillomas by Administration of Fruits of *Momordica dioica* Extract in DMBA/Croton Oil Induced Benign Cancer in Mice

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ABSTRACT

Skin papillomas are not cancerous, but they can trigger an inflammatory disorder and irritate the area where the wart is present. The study was to find natural agents that prevent and/or cure skin papillomas. The fruits of *Momordica dioica* have been known to contain potent phytoconstituents that have anti-inflammatory, cardiovascular, diabetic, oncological, and other health benefits. To investigate inhibition of skin papillomas by administration of a fruit extract of *M. dioica* in DMBA/Croton oil-induced benign cancer in mice. Induction of papilloma by topical application of DMBA/Croton oil for 4 to 5 weeks; after confirmation of papilloma's, the *M. dioica* and 5-Flu 10 mg/kg were administered. Body weight, tumor incidence, cumulative number of tumors, tumor yield, average latency time period, number of papillomas, hematological parameters, antioxidant enzymes, and pro-inflammatory cytokines were measured. In 100% tumor incidence was observed in DMBA/croton oil, whereas the other groups except the normal control had quite a similar tumor incidence. The cumulative number, tumor yield, and average latent period have significantly improved with the treatment in skin papilloma mice. Hematological markers and NLR (< 3.0) have improved ($p < 0.001$), which is indicative of reduced acute systemic inflammation. The deviations on lipid peroxidation (LPO) and catalase (CAT) from baselines were corrected by *M. dioica* and found to have a significant impact on their levels ($p < 0.001$). Post-treatment of immunosuppressive markers such as; transforming growth factor-β (TGF-β) ($p < 0.001$), tumour necrosis factor alpha (TNF alpha) ($p < 0.001$), and interleukin 6 (IL-6) ($p < 0.001$) were decreased significantly and increased the levels of IFG-g ($p < 0.001$), which correlates with increased immune activation. Hence, the intake of fruits of *M. dioica* inhibits the growth of skin papillomas.

Introduction

Skin cancer deaths are exceeding more in worldwide; data suggested the cancer is the 2nd most common cause of death after central venous system (CVS). Skin cancer is the most prevalent type of cancer in the United States, and around the world. The American Cancer Society reports that 87% of cancer is diagnosed in adults who are 50 years of age or older.[1] Skin cancer is a life-threatening disease in the USA and the cases are rapidly increasing due the immune compromise. Squamous cell carcinoma (SCC) is the second most prevalent skin cancer type and is characterized by aberrant, accelerated squamous cell proliferation. SCCs can manifest as elevated growths with central depression, scaly red patches, open sores, or rough, thickened, or wart-like skin. Precancerous lesions are where skin malignancies begin. Precancerous lesions are skin alterations that are not already cancer but may develop into it in the future. Papillomas are noncancerous, outward-growing benign growths that can be troublesome in particular areas.[2] They are not aggressive and do not spread. Papillomas can result in discomfort that calls for additional treatment, even though it's unlikely to reach malignant or life-threatening. Treatment for a papilloma lump or lesion depends on where it is and whether it

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is causing issues there. Warts can also be removed with medications like 5-Flu administered to cutaneous papilloma tissue.[3]

Cancer management is increasingly skewed towards elimination of the malignant cells by using surgery, chemotherapy and radiation are the primary protocol in cancer management. The immune system is an integral part and participates in the complex interplay between the treatment options and the cancer cells in the body. The immune system is responsible for keeping all diseases at bay and the advent of a disease is an indication of a compromised immune system. It is increasingly important to check for the immune status of the patient before the treatment and after each modality. Efforts to reset the immunological clock will help in a better prognosis of the disease and a sure predictor of relapse or recurrence of the disease.[4-10] This will help in framing an immunological reference grid in healthy *versus* diseased subjects and we could use this data for interspersing cellular immune-therapy in test groups who are subjected to the current standard and natural care approaches.

In a recent survey, 70% of cancer patients said they use complementary or alternative medicine as part of their cancer care. Throughout history, people from different nations have been used herbs, and India has one of the oldest, most varied, and rich cultural living traditions related to the use of medicinal plants.[11] For thousands of years, traditional medical systems relied on plants to treat ailments, and they still play a significant part in the basic healthcare of around 80% of the world's population.[12] Given that the remedies shown in the aforementioned examples are best found in nature, much emphasis should be paid to developing them for a world free of cancer.

The plant *Momordica dioica,* which can found all places including India, Pakistan, Bangladesh, the Himalayas, and Ceylon.[13,14] Over thousands of years, it has been used as a vegetable with high nutritional content as well as a preventative and therapeutic agent for a number of ailments.[15] The fruit includes diuretic, laxative, hepatoprotective, anti-inflammatory, anti-venomous, anti-leprosy, antihypertensive, anti-diabetic, anti-asthmatic, antipyretic, and antidepressant effects. Moreover, it also shows antioxidant activity, nephron-protective, neuroprotective, anti-allergic, anti-ulcer, anti-cancer, anti-microbial, anti-malarial, anti-fertility, and anti-epidemic activity.[16]

Many literatures have reported that plant-based compounds or phytoconstituents have the ability to produce therapeutic values in many diseases, including cancer, due to the presence of different kinds of phytochemicals that are considered suitable candidates for the anticancer and antioxidant effects of natural medicines. Here, the *M. dioica* extract was evaluated for DMBA/Croton oil-induced skin papillomas.

Materials And Methods

Collection and Preparation of Fruits of *M. dioica* for Extraction

We brought fresh *M. dioica* fruits from a local trader in Bangalore. A botanist, Dr. Geetanjali (HOD of the Botany Department, Sree Siddaganga College, Tumkur University, India), identified the fruits and reference number 141/17-18. The fruits were thoroughly cleaned before being chopped up and dried at room temperature in the shade. Using a blender, the plant material was ground into a coarse powder. The powder was used for the extraction.

Extraction of Fruits of *M. dioica* and Sample Preparation

The extraction was done as mentioned previously.[17] Briefly, it was done by using a soxhlet extractor. In the process of extraction, we used 100 g of *M. dioica* powder in 1000 mL of methanol in a reflux condenser for 3 cycles over 7 hours. Later it was taken out, filtered, and dried at room temperature.

Experimental Animals

The study was carried out using adult male albino mice weighing 24 ± 2 g. Prior to the experiment, they were acclimated for a week. The protocol was properly authorized by the IAEC of the Karnataka College of Pharmacy, Bangalore, (IAEC Sl. No: KCP/IAEC/11/22-23/02/22/12/22) and all animal studies were carried out in compliance with the CPCSEA.

Acute Toxicity Studies for Dose Fixation

As previously reported,[18] the dose of 250 and 500 mg/kg were chosen.

Experimental Design

The selection of animals is mentioned below. The skin back hairs of mice were shaved at 3x3 cm^2 at least 3 days before starting drug applications.

Group-1: [Normal Saline treated mice (Normal control)]

This group's animals (N = 6) received normal saline (10 mL/kg b.w.), standard food, and access to water every day.

Group-2: [DMBA/Croton oil (Disease control)]

In this group of animals (N = 10), a single dose of DMBA (100 g/100 L of acetone) was applied as an initiator to a shaved portion of the mice's skin. Croton oil (1% in 100 mL of acetone) [19] was used three times a week as a promoter over the following 4 to 6 weeks, or until skin papillomas appeared.

Group-3: [5-Fluorouracil (10 mg/kg body weight) – Standard drug]

In this group of animals (N = 10), received 5-fluorouracil (10 mg/kg b.w, S.C. two times a week)[20] for 3 weeks after

confirmation of skin papilloma's [DMBA + Croton oil, same as group 2].

Group-4: [M. dioica orally (250 mg/kg.b.w)- Test drug]

Animal (N = 10) in this group received *M. dioica* (250 mg/kg.b.w/day) orally for 3 weeks after confirmation of skin papilloma's [DMBA + Croton oil, same as group 2].

Group-5: [M. dioica orally (500 mg/kg.b.w.)- Test drug]

Animal (N = 10) in this group received *M. dioica* (500 mg/kg.b.w/day) orally for 3 weeks after confirmation of skin papilloma's [DMBA + Croton oil, same as group 2].

Group-6: [M. dioica orally (500 mg/kg.b.w.)] + [Topically Application – Test drug]

Animal (N = 10) in this group received *M. dioica* (500 mg/kg.b.w/day) orally + Topical application (0.5 mL) on the affected area for 3 weeks after confirmation of Skin papilloma's [DMBA + Croton oil, same as group 2].

Parameters of the Study

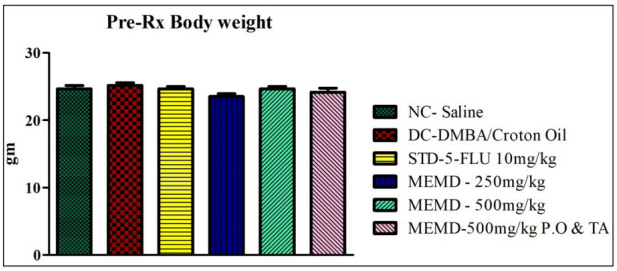
During the experimentation, mice of all the treated and untreated groups were carefully examined once a week for skin papillomas and these were recorded in a database and also the below markers were put into account.

Morphological estimation

Body weight, tumor incidence cumulative number of papillomas, tumor yield, and average latent period were measured, and the method was followed as previously reported. [19]

Pictograph image

Every week have taken an image to compare the Skin papilloma's from the baseline and disease control group. At the end of the experiment, blood was obtained via heart puncture or retro-orbital under light anesthesia with pentobarbitone sodium and used for the assessment of hematological markers,[21,22] neutrophils and lymphocyte ratio (NLR) and pro-inflammatory cytokines.



Values are expressed as Mean ± SEM, (n = 10 mice in each group). $^{ns}p > 0.05$ between all the groups.
NC- Normal Control, STD- Standard drug, DC-Disease control, FLU- Fluorouracil, MEMD-Methanolic extraction of *M. dioica,* P.O- Oral, TA-Topical application

Fig. 1: Effect on body weight before treatment of *M. dioica* against DMBA/Croton oil induced skin cancer in mice

Biochemical estimation

Biochemical analyses were performed on skin tissues from each group of experimental animals. The homogenate of skin tissues was centrifuged at 1000 g for 5 minutes, and the supernatant was used for the test of:-

- *Lipid peroxidation assay*

Ohkawa *et al.*[23] method was used to calculate lipid peroxide levels. To summarise, thiobarbituric acid (0.8%), sodium dodecyl sulfate (0.1%), and acetic acid (20%) were added to 100 ml of the above-mentioned tissue homogenate (10%). After heating for 30 minutes, the mixture was cooled, and extracted with N-butanol-pyridine, and the OD of MDA was measured at 532 nm. MDA content is given as nmol/mg protein.[24]

- *Catalase assay*

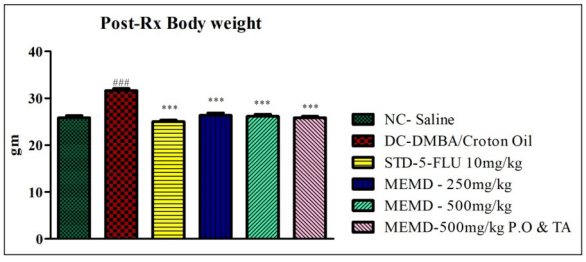
This was tested using the Aebi method,[25] 30 mM H2O2 to 100 mL of supernatant (10% of tissue homogenate) in 50 mM PBS, pH 7. The absorbance was measured by using UV at 240 nm. The enzyme's activity is measured in units per milligram of protein, with 1 U equalling 1 mol of H_2O_2/ mg/min/mg protein.[26]

- *Pro-inflammatory cytokines*

The protein content in plasma was normalized using the Lowry *et al.* technique. TNF-alpha, IFN-g, IL-6, and TGF-beta concentrations were evaluated using a sandwich ELISA assay with commercial kits, and A 450 nm was quantified using an ELISA reader.[27,28]
A standard calibration graph (Abs vs. Conc.) was plotted, and the concentrations of unknown samples were calculated using the graph.

Statistical Analysis

The data are shown as the Mean ± SEM of N = 10 mice in each group. GraphPad Prism version 5 statistical software was used to evaluate the data. The significance of the difference between groups was determined using a one-way analysis of variance (ANOVA) followed by Tukey's test, with $p < 0.05$ considered significant when comparing normal control (untreated) *vs.* all groups.



Values are expressed as Mean ± SEM, (n = 10 mice in each group). $^{###}p < 0.001$ compared to normal control, $^{***}p < 0.001$ compared to disease control, DMBA/ Croton Oil

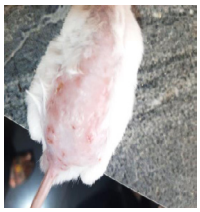
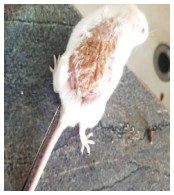
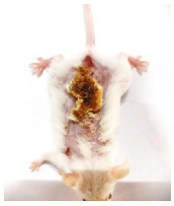
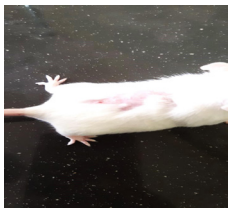
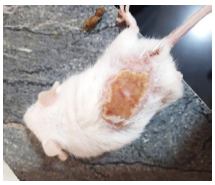
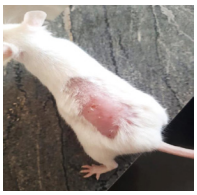
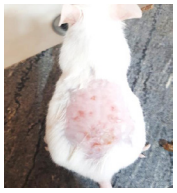
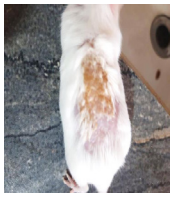
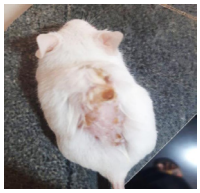
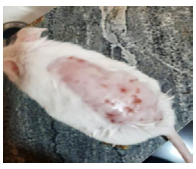
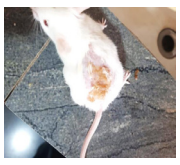
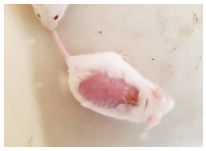
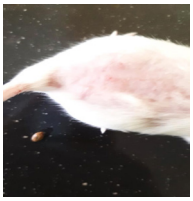
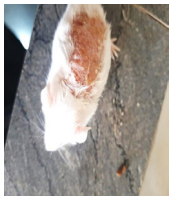
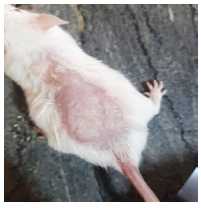
Fig. 2: Effect on body weight after treatment of *M. dioica* against DMBA/Croton oil induced skin cancer in mice

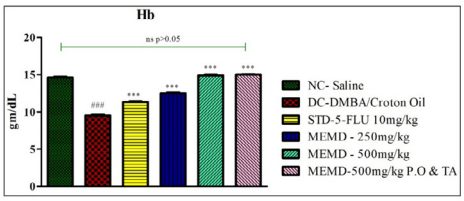
Table 1: *In-vivo* parameters for *Momordica dioica* efficacy against DMBA/Croton oil-induced skin cancer

Group initial		Body weight (gm)		Tumor incidence (%)	Cumulative of no's tumors	Tumor yield	ALP < 2	No. of papilloma with tumor size (mm)		
		Final						2-4	4 >	
1	Normal saline treated mice (Normal control; 10 mL/kg.b.w)	24.67 ± 0.49	25.83 ± 0.48	-	-	-	-	-	-	-
2	DMBA/Croton oil (disease control)	25.17 ± 0.4	31.67 ± 0.42	100	32	8	6.5	15	10	7
3	5-Fluorouracil (10 mg/kg body weight) - STD	24.7 ± 0.33	25.0 ± 0.37	80	3	7	3.2	2	1	-
4	*M. dioica* orally (250 mg/kg.b.w)	23.50 ± 0.43	26.33 ± 0.56	90	4	8	4.3	3	1	-
5	*M. dioica* orally (500 mg/kg.b.w)	24.6 ± 0.33	26.17 ± 0.4	85	2	8	3.5	2	-	-
6	*M. dioica* orally (500 mg/kg.b.w) + Topical application (0.5 mL)	24.17 ± 0.6	25.83 ± 0.3	80	1	7	1.5	1	-	-

Values are expressed as Mean ± SEM, (n = 10 mice in each group)

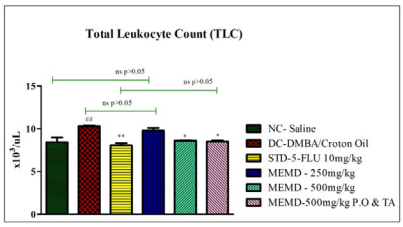
Fig. 3: Pictograph illustrating *M. dioica* efficacy activity against DMBA/Croton oil-induced skin cancer in mice

Group	1^{st} Week	4^{th} Week (0 Day of Treatment)	8^{th} Week (30 Day of Treatment)
DMBA/Croton oil (Disease control) DMBA (100 g / 100 L of acetone), croton oil (1% in 100 mL of acetone)			
5-Fluorouracil (10 mg/kg body weight S.C.) - STD			
M. dioica (250 mg/kg.b.w,p.o)			
M. dioica (500 mg/kg.b.w, p.o.)			
M. dioica (500 mg/kg.b.w, p.o.) + Topical application			



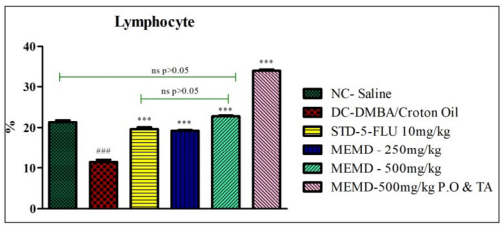
Values are expressed as Mean ± SEM, (n = 10 mice in each group). ###p < 0.001 compared to normal control, ***p < 0.001 compared to disease control, DMBA/Croton Oil, nsp > 0.05 between the normal control vs MEMD 500 mg/kg p.o. and TA

Fig. 4: Effect on Hb after treatment of *M. dioica* against DMBA/Croton oil induced skin cancer in mice



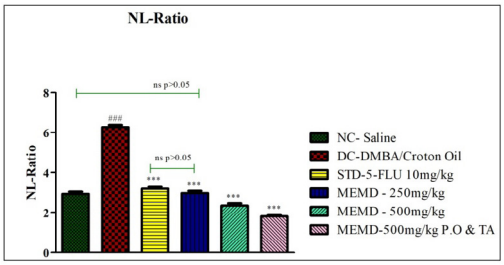
Values are expressed as Mean ± SEM, (n = 10 mice in each group). ##p < 0.01 compared to normal control, **p < 0.01, *p < 0.05 compared to disease control, DMBA/Croton Oil, nsp > 0.05 between the Normal control vs MEMD 250mg/kg p.o, 5-Flu vs MEMD 500 mg/kg p.o. and TA, and DMBA/Croton oil vs MEMD 250mg/kg,p.o

Fig 5: Effect on WBC after treatment of *M. dioica* against DMBA/Croton oil induced skin cancer in mice



Values are expressed as Mean ± SEM, (n=10 mice in each group). ###p < 0.001 compared to normal control, ***p < 0.001 compared to disease control, DMBA/Croton Oil, nsp > 0.05 between the normal control vs MEMD 500mg/kg p.o, 5-Flu vs MEMD 500 mg/kg p.o.

Fig. 6: Effect on Lymphocyte after treatment of *M. dioica* against DMBA/Croton oil induced skin cancer in mice



Values are expressed as Mean ± SEM, (n = 10 mice in each group). ###p < 0.001 compared to normal control, ***p < 0.001 compared to disease control, DMBA/Croton Oil, nsp > 0.05 between the normal control vs MEMD 250mg/kg p.o, 5-Flu vs MEMD 250 mg/kg p.o.

Fig. 7: Effect on NLR after treatment of *M. dioica* against DMBA/croton oil induced skin cancer in mice

Results And Discussion

Uncontrolled cell growth can lead to tumors, immune system damage, and other potentially lethal complications. Cancer can affect a variety of parts of the body, including the breasts, lungs, prostate, and skin. Natural endogenous phytochemicals exhibit an active cancer prevention strategy and/or alternative or adjuvant therapy by inhibiting, delaying, or reversing human carcinogenesis. Certain dietary phytochemicals have been shown in studies to have cancer-protective properties when mediated by carcinogens. *M. dioica* fruits are a medical herb and have been used as common vegetables in the human diet since time immemorial and thus could be regarded safe and it has been reported in many literatures.[29]

The body weight of DMBA/Croton oil treated animals was found to be increased p < 0.001 compared to normal rats. Test drug (*M. dioica*) treated decreased the body weight near normal values, oral + topical drug administration produced more better results compare to only oral and topical, only oral produced better results than only topical drug administration (Figs 1 and 2).

As reported previously,[30] the lesions in the positive control developed as distinct, tiny, smooth, pink-red, confined, multicentric single nodules that progressed in size and number with the application of DMBA solutions. Similarly, in our experiment, we have observed in the same manner, increased cumulative papillomas, tumor yield, and latent period with the application of DMBA/Croton oil. The effect of *M. dioica* fruit extract on multiple aspects of skin cancer associated with DMBA/Croton oil (Table 1 and Fig. 3).

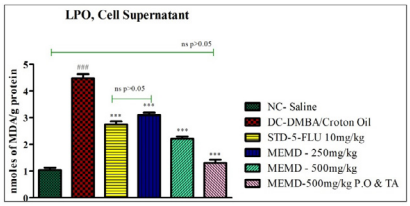
The chemopreventive action of *Curcuma longa* extract[30] against DMBA-induced tumorigenesis may be related to the antioxidant and anti-inflammatory functions of certain of its ingredients, as the induction of tumors through DMBA is mediated *via* the production of free radicals products and oxidative DNA damage (Plummer *et al.*, 2001). The fact that the incidence of tumors in rats treated with fruits of *M. dioica* extract does not increase as long as the treatment is sustained lends support to this indication. Elevated levels of hematological markers (Hb, WBC, and Lymphocytes) and NLR are associated with the application of DMBA/Croton oil. And reduction in these markers with the administration of *M. dioica* extract is indicative of a sub-optimal immune environment (Figs 4 to 7).

Oxidative stress has been shown to harm DNA molecules, change signaling pathways, and control the development of many malignancies. The imbalance between the generation of reactive metabolites and free radicals and their elimination by antioxidant defense systems is known as reactive oxygen species (ROS). This imbalance causes harm to vital cells and biomolecules, which could have an effect on the entire organism. The production of ROS in the skin causes oxidative stress, which has been linked to the development of skin cancer. Finding decreased skin

catalase and higher lipid peroxidation (LPO) activity may be accountable for the increased oxidative stress exposure. This has been seen in the positive control group but the treatment of extracts showed a positive character towards these markers which is a good sign for this plant (Figs 8 and 9).

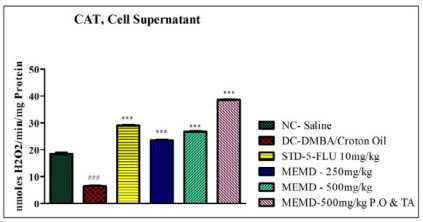
Tumour Necrosis Factor alpha (TNF alpha), interleukin 6 (IL-6), and transforming growth factor-β (TGF-β) are examples of inflammatory cytokines that have been linked to oxidative stress-induced inflammation. Alterations in the expression of particular microRNAs have also been documented. This chronic inflammatory and oxidative milieu creates a vicious loop that may affect surrounding healthy epithelial and stromal cells and may eventually lead to carcinogenesis.[31-34] Interferon gamma (IFN-g) may also play major and significant pro-tumor roles during the equilibrium and escape stages. These IFN-g effects, which at first sight seem to contradict one another, unquestionably have a significant impact on both the induction of the inflammatory response to cancer and the course of the disease. An increase in TGF-beta, TNF-α and the presence of IL-6 in the positive control group indicates an immunosuppressive environment. These levels were elevated with the treatment of *M. dioica* groups (Figs 10-13). Increased INF-g levels indicate immuno-protection and improved outcomes (Fig. 11).

Transient increases in these levels can be linked to the cytotoxic effect of treatments. However, the levels should be closely monitored as chronic elevation of



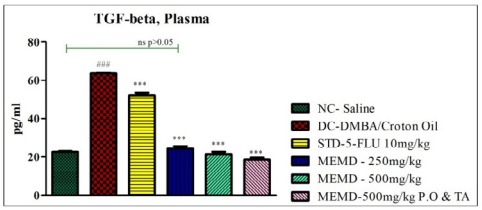
Values are expressed as Mean ± SEM, (n = 10 mice in each group). $^{###}p < 0.001$ compared to normal control, $^{***}p < 0.001$ compared to disease control, DMBA/Croton Oil, nsp > 0.05 between the Normal control vs MEMD 500 mg/kg p.o. and TA, 5-Flu vs MEMD 250 mg/kg,p.o

Fig. 8: Effect on LPO study for anti oxidant enzyme efficacy of *M. dioica* against DMBA/Croton oil induced Skin Cancer



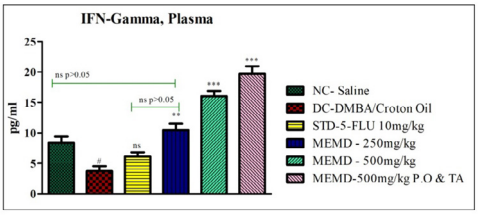
Values are expressed as Mean ± SEM, (n = 10 mice in each group). $^{###}p < 0.001$ compared to normal control, $^{***}p < 0.001$ compared to disease control, DMBA/Croton oil.

Fig. 9: Effect on CAT study for anti-oxidant enzyme efficacy of M. dioica against DMBA/Croton oil induced skin cancer



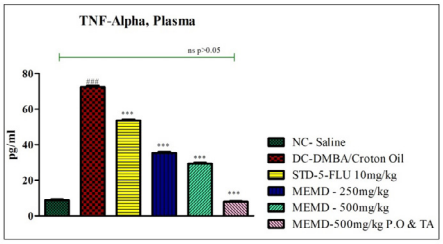
Values are expressed as Mean ± SEM, (n = 10 mice in each group). $^{###}p < 0.001$ compared to normal control, $^{***}p < 0.001$ compared to disease control, DMBA/Croton oil, nsp > 0.05 between the normal control vs MEMD 250 mg/kg p.o.

Fig. 10: Effect on TGF-B study for pro-inflammatory cytokine impact of *M. dioica* against DMBA/Croton oil induced skin cancer



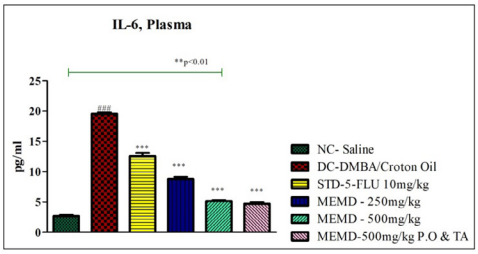
Values are expressed as Mean ± SEM, (n = 10 mice in each group). #p < 0.05 compared to normal control, ***p < 0.001, **p < 0.01 compared to disease control, DMBA/Croton oil, nsp > 0.05 between the normal control vs MEMD 250 mg/kg p.o, 5-Flu vs MEMD 250 mg/kg p.o. and DMBA/Croton oil vs 5-Flu.

Fig. 11: Effect on IFN-G study for pro-inflammatory cytokine impact of *M. dioica* against DMBA/Croton oil induced skin cancer



Values are expressed as Mean ± SEM, (n = 10 mice in each group). $^{###}p < 0.001$ compared to normal control, $^{***}p < 0.001$ compared to disease control, DMBA/Croton Oil, nsp > 0.05 between the normal control vs MEMD 500 mg/kg p.o, and TA.

Fig. 12: Effect on TNF-A study for pro-inflammatory cytokine impact of *M. dioica* against DMBA/Croton oil induced skin cancer



Values are expressed as Mean ± SEM, (n = 10 mice in each group). $^{###}p < 0.001$ compared to normal control, $^{***}p < 0.001$ compared to disease control, DMBA/Croton Oil, $^{**}p > 0.01$ between the normal control vs MEMD 500 mg/kg p.o

Fig 13: Effect on Il-6 study for pro-inflammatory cytokine impact of M. dioica against DMBA/Croton oil induced Skin Cancer

these inflammatory markers is linked with poor overall outcomes. It should also be noted that these biomarkers are dynamic in nature and can change with tumor stage and treatment status. As a result, it can be said that regular use of *M. dioica* lowers the frequency of skin tumors and may open the door to the development of plant-based anticancer medications.

Conclusion

Our results conclusively support our hypotheses by showing that *M. dioica* can inhibit the progression of benign tumors. It has shown that continuous intake of plant extract reduced the incidence of papillomas in treated groups. It was confirmed further supported by the pictograph of the treated groups and disease control group where have seen completely off the papillomas in group VI (*M. dioica* 500 mg/kg oral + Topical administration). *M. dioica* inhibits the generation of free radicals by suppressing the levels of LPO and increases the levels of CAT across all treatment groups. *M. dioica* was also shown to bring down the levels of pro-inflammatory cytokines like; TGF-beta, TNF-alpha and IL-6 cytokine levels, and IFN-g brought to be normal. *M. dioica* predominantly comprises potent phytochemicals such as saponins, triterpenoids, alkaloids, flavonoids, and polyphenols which are under study for their future employment in integrative oncology and non-oncology studies.

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Authors Contributions

All the authors contributed to the preparation of the final manuscript.

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