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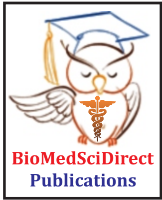

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Original Article

Inhibition of dimethylebenz (a) anthracene (DMBA)/croton oil induced skin tumorigenesis in Swiss albino mice by *Aloe vera* treatment.

Geeta Chaudhary

Jyoti Parmar, Preety Verma and Pradeep Kumar Goyal

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ABSTRACT

In the present study, anti-cancer property of *Aloe vera* was evaluated against 7,12-dimethyl benz(a)anthracene (DMBA) induced skin tumorigenesis in Swiss albino mice. A single topical application of 7,12-dimethyl benz(a)anthracene (100 µg/100 µl of acetone), followed 2 weeks later by repeated application of croton oil (1% in acetone three times a week) for 16 weeks exhibited 100 percent tumor incidence (group III). In contrast, animals treated topically with *Aloe* gel (group IV) or orally with *Aloe* extract (group V) and topical with Aloe gel + orally with extract (group VI) exhibited 40, 50 and 20 per cent tumor incidence, which significantly higher than 100% tumor incidence in the group III (control). The cumulative number of papillomas during the observation period of 16 weeks was significantly decreased in the Aloe treated groups IV, V and VI (4, 5 and 2 in Aloe gel, Aloe extract, and Aloe gel + Aloe extract treated animals respectively) in compare to 36 cumulative number of papillomas in carcinogen control group. The average latent period significantly increased from 4.9 weeks in the control group to 5.3, 6.4 and 6.5 weeks in all Aloe treated groups. The tumor burden and tumor yield were significantly lesser (1.33, 1.25 and 1.0 and 0.4, 0.5 and 0.2) as compared to DMBA/ croton oil treated control (3.6 and 3.6). Furthermore, the level of lipid peroxidation was significantly lesser than in the control animals (group III) in skin. In addition, depleted levels of reduced glutathione (GSH), DNA, catalase and protein were restored in *Aloe*-treated groups. The study has revealed the inhibition of dimethylebenz (a) anthracene (DMBA)/croton oil induced skin tumorigenesis in Swiss albino mice by *Aloe vera* treatment.

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1. Introduction

Cell division or cell proliferation is a physiological process that occurs orderly and controlled in almost all tissues and makes balance between proliferation and programmed cell death tightly to ensure the integrity of organs and tissues. However, if this process becomes uncontrollable for some reason then cells will continue to divide and develop into a lump, which is called a tumor. Initiation or generation of cancer is the process of derangement of the rate of cell division due to damage to DNA, which may be caused by external exposure of body to chemicals, radiation or even infectious agents (viruses) [1-5].

Even before the development of guidelines for nutrition and cancer prevention by the American cancer Society, researchers began to investigate several substances that have the potential to inhibit tumor formation. This investigation evolved into what is called "chemopreventive strategy" for cancer prevention.

Chemoprevention is one of the best strategies of cancer prevention which was first defined by Sporn in 1979[49]. It refers to the use of synthetic, chemicals or natural products, which help in cancer prevention. A large number of synthetic compounds have been tested to prevent cancer but most of them was found to die. A moderately effective compound with little toxicity can be more useful than a potent chemopreventive agent with high toxicity for individuals who are at risk of cancer. Naturally occurring antioxidants such as vitamins, micronutrients and other plant products are nontoxic or markedly lesser toxic than synthetic chemopreventive agents and are constituents of human diet.

* Corresponding Author : Dr. Geeta Chaudhary
Radiation and Cancer Biology Laboratory,
Department of Zoology,
University of Rajasthan,
Jaipur, India.
Email: falak.geet@rediffmail.com

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Herbal medicines are the oldest remedies known to mankind. Herbs had been used by all cultures throughout history but India has one of the oldest, richest and most diverse cultural living traditions associated with the use of medicinal plants [11].

Plants have formed the basis for the treatment of diseases in traditional medicine systems for thousands of years and continue to play a major role in the primary health care of about 80% of the world's inhabitants [18].

Naturally occurring phytochemicals display an active cancer preventive strategy to inhibit, delay, or reverse human carcinogenesis. Studies have indicated that certain daily-consumed dietary phytochemicals have cancer protective effects mediated by carcinogens.

Aloe vera is an herb and belongs to family Lilliaceae. Its leaf contains two basic components, Aloe gel (AG) and latex. Aloe gel is a thin clear jelly like substance obtained from the parenchymal tissue of inner portion of leaf. It contains glucomannan, acemannan, magnesium, glucose, gamma-linolinic acid, saponins, sterols, and cholesterol [2, 14, 17]. It is effective in the treatment of radiation induced burns [13, 20].

AG also contains lignin, salicyclic acid, saponins sterols and terpenoids. The fresh gel contains the photolytic enzyme carboxy peptidase (which breaks down bradykinin), glutathione peroxidase, as well as several isozymes of superoxide dismutase [26, 42].

Gel is also rich in vitamin A (ß-carotene) C, E and B12, thiamine, niacin and folic acid, as well as minerals like sodium, potassium, zinc, chromium, selenium,calcium, and iron [6, 34, 46, 52].

Aloe has multiple biological activities such as anti-bacterial and anti-fungal [3, 10], anti-radiation [41], anti-inflammatory [40, 51], wound healing [13], anti-oxidant [28] and immunomodulatory [29]. Anti- inflammatory compound, c- glucosyl chromone has been isolated from Aloe gel [22]. Therefore, the present study is undertaken to obtain insight into the possible anti-cancer activity of Aloe vera against DMBA-induced skin tumorigenesis in mice.

2. Materials and Methods

2.1. Animals

Adult 7-8 weeks old male Swiss albino mice weighing 24±2 g were used for conducting this study. Four animals were housed in one polypropylene plastic cage containing saw dust (procured locally) as bedding material. They were maintained under control conditions of temperature (25±2°c) and light (14 light: 10 dark). The animals were provided standard mice feed, procured from Aashirwad Industries, Chandigarh (India), and water ad libitum. As a precaution against infections, tetracycline water was given to animals once in fortnight. Three days before the commencement of experiment, hair on the back of the mice were clipped in 3 X 3 cm^2 area. Only those mice showing no hair growth were used for the present study.

2.2. Chemicals

Initiator, 7, 12 – Dimethylbenz (a) anthracene (DMBA) and promoter (Croton oil) were procured from Sigma Chemical Co., St. Louis, USA.

2.3. Preparation of test substance (*Aloe ver*a extract and gel)

Aloe vera extract

Plant material (Aloe vera leaves) was collected locally after its proper identification by a competent Botanist, Department of Botany, UOR, Jaipur (Voucher No RUBL 1986). The cold extract of fresh and shade dried leaves of Aloe was prepared in ethyl alcohol. For this purpose, Aloe leaf powder was mixed with double the volume of absolute ethyl alcohol. The mixture was stirred and left for 24 hrs. and then filtrated through cheese cloth. The left over residue after filtration was again mixed with same volume of ethyl alcohol as used earlier and the procedure was repeated two more times. Finally, all three filtrates were mixed and the alcohol was allowed to evaporate naturally from it at room temperature (30 3C) to obtain a concentrated powder of Aloe extract (0.8%), which was placed in oven at 40c for complete evaporation of alcohol. The powdered extract was redissolved in double distilled water (DDW) at the time of oral administration to experimental animals.

Aloe gel

Aloe gel was prepared from the fresh fleshy leaves. The green layer of a leaf was peeled off and transparent pulp was obtained, homogenized and passed through cheese-cloth. The resulting pulp was stored at 4ºC and used for topical application to experimental animals.

2.4. Experimental Design

Skin of 3 X 3 cm^2 back area of animals was shaven three days before the commencement of experiment, and only those animals in the resting phase of hair cycle were selected for the study. A total of 60 selected animals were randomly divided into six groups (I, II, III, IV, V & VI) to evaluate chemopreventive role of Aloe against DMBA/ croton oil induced skin papillomagenesis.

Group I [DDW treated mice (normal)]

Mice (N=10) of this group were given DDW (10 ml/kg body weight), a normal diet and tap water ad libitum daily. After 16 weeks, mice were autopsied and the skin of dorsal area (3 X 3 cm2) was taken for the biochemical and histopathological studies.

Group II

Mice (N=10) of this group treated topically with Aloe gel, orally with Aloe extract and topically with Aloe gel + orally with Aloe extract for 16 consecutive weeks and were used to study the macroscopic tumorigenic effects, biochemical and histopathological changes induced by Aloe alone treatment (gel and extract) if any.

Group III

A single dose of DMBA (100g / 100l of acetone) over 3 X 3 cm^2 shaven area of the mice skin. Two weeks later, croton oil (1% in 100l of acetone) was applied, as a promoter three times in a week animals of this group. The end of experiment i.e.16 weeks, which served as carcinogen control group

Group IV

Aloe gel (1 ml / 9 cm^2/mouse/day) was applied topically on the 10 animals of this group two weeks before of DMBA (100 g/ 100l of acetone) application and was followed by the topical application of croton oil (1% in 100l of acetone thrice a week) till the end of experiment i.e.16 weeks with a gap of 2 hours after DMBA and every croton oil application.

Group V

Animals (N = 10) of this group were treated with Aloe vera extract (AVE) (1000 mg/kg b .wt./day) orally treatment starting from two weeks prior to DMBA (100 g/ 100l of acetone) and followed by the application of croton oil (1% in 100l of acetone thrice a week) till the end of experiment i.e.16 weeks.

Group VI

During the period of 16 weeks of experimentation, mice of all groups were weighed carefully examined once a week skin papillomas and these were recorded. The following parameters were taken into consideration:

(a) Tumor study

Body weight: Change in mean body weight was measured weekly.
Tumor incidence: The number of mice carrying at least one tumor expressed as percent incidence.
Cumulative number of papillomas: Total number of tumors bearing mice.
Tumor yield: The average number of papillomas per mouse.
Tumor burden: The average number of tumors per tumor bearing mouse.
Tumor diameter: Average diameter of tumors.
Tumor weight: Average weight of tumors recorded at the termination of experiment.

2.5. Average latent period

The lag between the application of the promoting agent and the appearance of 50% tumors was determined. 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 total number of tumors

$$\text{Average latent period} = \frac{\sum fx}{n}$$

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

2.6. Biochemical Study

Skin was removed from the selected dorsal area for biochemical study soon after the sacrifice of animals. Small pieces of skin were taken and crushed in masticator. Homogenates were prepared in Tris KCl, 10 per cent TCA, phosphate buffer and 30 percent KOH for estimation of LPO, GSH, DNA, catalase activity and total proteins contents respectively.

2.6.1.Lipid peroxidation (LPO) assay

GSH level was measured by the method of Moron [32] and absorbance was read at 412 nm by using UV-VIS Systronic spectrophotometer. The level of GSH is expressed as μM/g.

2.6.3.DNA contents

The amount of DNA was estimated by the method of Burton [12]and absorbance was read at 640 nm. The DNA contents were expressed as mg/gm of tissue taken.

2.6.4.Catalase activity

Catalase activity was measured by the method of Aebi [1] and absorbance was read at 210 nm by using UV-VIS Systronic spectrophotometer. The activity of the enzyme is expressed as μmol of H_2O_2 reduced /mg protein/minute.

2.6.5.Total protein contents

Total protein contents were measured by the method of Bradford [9] using bovine serum album as a standard and absorbance was read at 595 nm by using UV-VIS Systronic spectrophotometer. Total protein contents were measured as nM/mg.

2.7.Statistical Analysis

The results are expressed as the mean standard error of the mean or as a percentage. The data from biochemical determinations were analyzed using the Student t test.

3. Results

The findings of the present study are depicted in Tables 1-2 and Figures 1-11. Animals of Group- III (control) in which a single topical application of DMBA, followed by croton oil produced skin papillomas, which started appearing from the 6th week onwards. The incidence in DMBA/croton oil treated mice (carcinogen control) reached 100% by the termination of the experiment (i.e. 16 weeks).

In the skin papilloma model, significant prevention of tumor incidences was observed in the Aloe gel, Aloe extract and Aloe gel + extract treated experimental groups (40, 50 and 20 % in groups IV, V and VI respectively) as compared to carcinogen control (100 %) group. The cumulative number of papillomas was also reduced in the Aloe gel, Aloe extract and Aloe gel + extract treated experimental groups (4, 5 and 2 in groups IV, V and VI respectively) as compared to carcinogen control (100 %) group.
The tumor burden and tumor yield were significantly decreased (1.33, 1.25 and 1.0 and 0.4, 0.5 and 0.2) as compared to DMBA treated control (3.6 and 3.6) group.

Average latency period was significantly increased with Aloe gel, extract and Aloe gel + extract treatment (5.3, 6.4 and 6.5 respectively) in compared to carcinogen control group (4.9).

Significantly lower reduced glutathione (GSH), DNA, catalase, and protein activity was noted in the skin of carcinogen control mice (group III) as compared with Aloe treated experimental animals (groups IV, V, and VI) at the time of termination of the experiment (ie,16 weeks). Treatment with Aloe vera resulted in enhanced levels of GSH (P □□.05), DNA (P □□.05), catalase (P □ .05), and protein (P□□.05) in these groups. A considerable elevation of LPO level was noted in the skin after DMBA and croton oil treatment, whereas administration of A. vera (P □□.05) significantly reduced the level of LPO in all the Aloe treated experimental groups (IV, V, and VI) in comparison with the carcinogen control group.

Table-1. Inhibition of dimethylebenz (a) anthracene (DMBA)/croton oil induced skin tumorigenesis in Swiss albino mice by *Aloe vera* treatment.

Group	Body Weight % Initial Final	Tumor incidence %	Cumulative Number of Tumors	Tumor yield	Tumor burden	A.L.P	Number of papillomas with tumor size (mm) <2	2- 4	> 4
I (n=10)	100	110	–	–	–	–	–	--	–
II (n=10)	100	115	–	–	–	–	--	_	–
III (n=10)	100	87.5	100	36	3.6	4.9	20	13	3
V(n=10)	100	91.25	40	4	0.4	5.3	4	_	-
V(n=10)	100	91.00	50	5	0.5	6.4	4	-	-
VI (n=10)	100	97.25	20	2	0.2	6.5	2	-	-

Table-2. Inhibition of dimethylebenz (a) anthracene (DMBA)/croton oil induced skin tumorigenesis in Swiss albino mice by Aloe vera treatment.

Group	Lipid peroxidation (n mol/mg	Reduced glutathione (µM/g)		DNA level (mg/gm)	Catalase (µmolof H_2O_2 reduced /mg protein/minute)	Protein (nM/mg)
I (n=10)	2.81±0.08	19.69±0.50	46.34±1.05	46.34±1.05	57.23±0.39	81.71±1.86
II (n=10)	2.79±0.07	19.98±0.50	47.56±0.0	47.56±0.0	64.86±0.98 NS	82.64±1.86
III (n=10)	3.85 ± 0.04*	10.58±0.88*	30.89±0.55*	30.89±0.55*	50.70±1.31*	56.78±1.86*
V(n=10)	3.34± 0.04*	12.64±0.50*	35.75±0.95*	35.75±0.95*	54.07±0.98*	35.75±0.95*
V(n=10)	3.26± 0.04*	14.81±0.50*	43.29±0.59*	43.29±0.59*	56.16±0.57*	43.29±0.59*
VI (n=10)	2.96± 0.49	16.50±0.43*	45.73±0.0*	45.73±0.0*	60.14±0.12*	45.73±0.0*

Each value represents = Mean ± SE

Significance level = *p < 0.05

Figure 1. Body weight (%) in mice treated with DMBA/ croton oil with or without topical application of Aloe gel / or oral administration of extract.

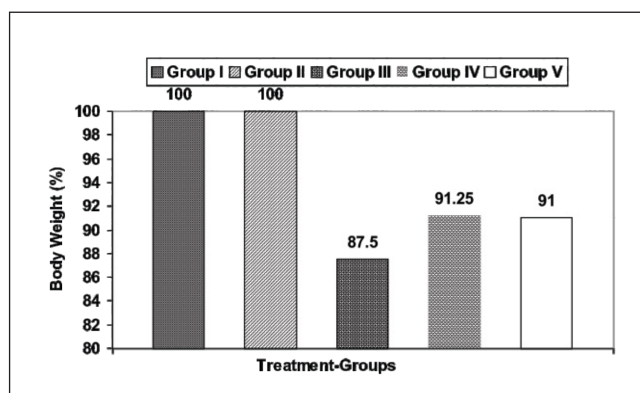


Figure 2. Tumor (% incidence) in mice treated with DMBA / croton oil in mice wit or without topical application of Aloe gel and / or oral administration of extract.

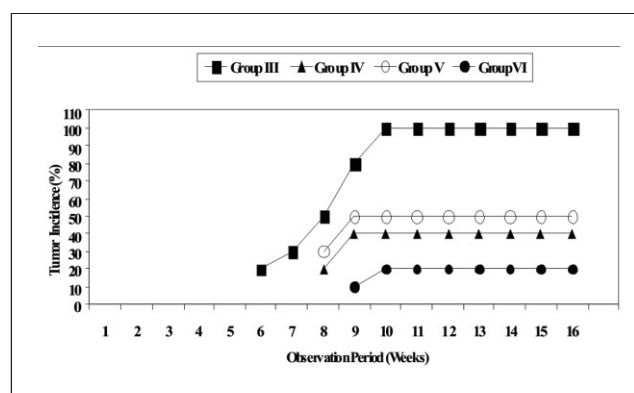


Figure 3. Cumulative number of papillomas in micetreated with DMBA / croton oil with or without topical application of Aloe get and / or oral administration of extract.

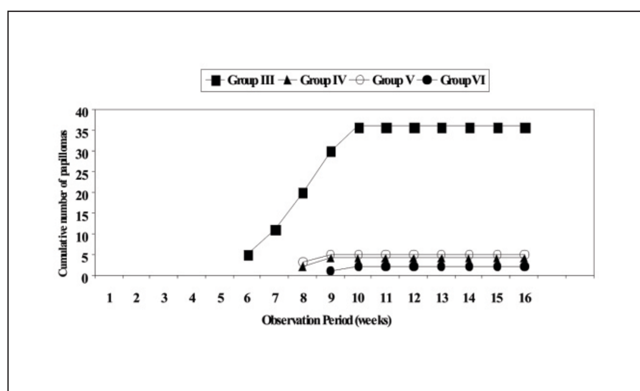


Figure 4. Tumor yield mice treated with DMBA/ croton oil with or without topical application of Aloe gel and / or oral administration of extract.

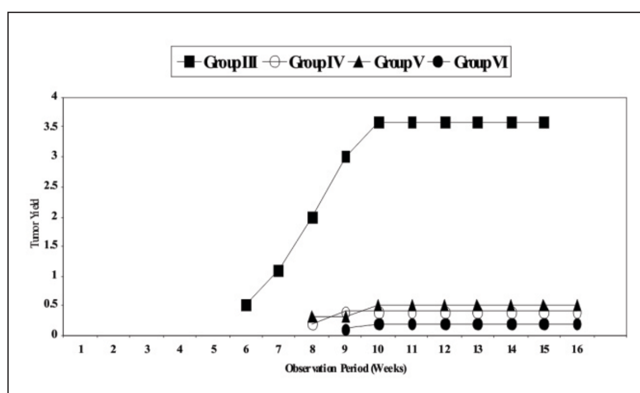


Figure 5. Tumor burden in mice treated with DMBA / croton oil with or without topical application of Aloe gel and / or oral administration of extract.

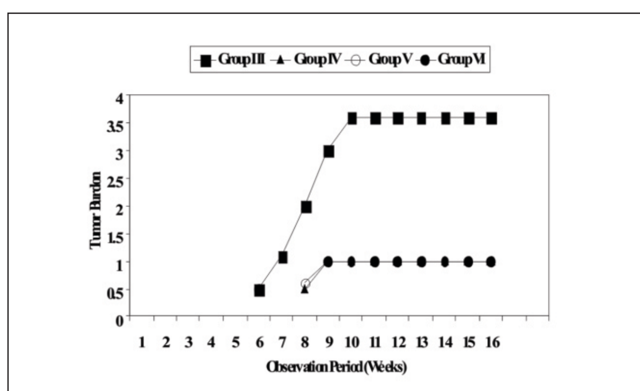
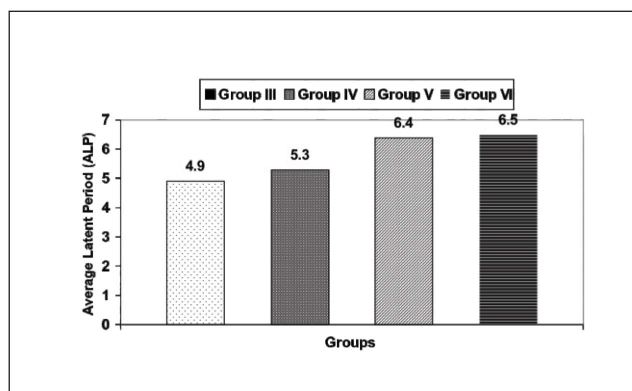


Figure 6. Average laten period (in weeks) in mice treated with DMBA / Croton oil with or without topical application of Aloe gel and / or extract.



4. Discussion

The induction of cancer (carcinogenesis) is a multistage process and depends on inherited and acquired susceptibility factors, on exposure to initiation factors, i.e., exogenous and endogenous carcinogens, and on promotion and progression factors.

Skin tumor initiation by chemical carcinogens such as DMBA appears to be an irreversible stage that probably involves a somatic mutation, mainly in the Ha-ras oncogenes [4, 47, 48].

The prevention of cancer, namely inhibition or reversal of carcinogenesis, may be conducted at variety of time points in this process to reduce occurrence of in situ or invasive cancers or cancer morbidity and/or mortality. While it is generally accepted that a diet of large amounts of vegetables, fruits, and other plant products lowers cancer incidence, however, there is still a need to identify the most effective constituents of the diet as well as to elucidate their mechanisms of action. Currently, most people are exposed to different combinations of agents. Because many of those compounds are taken orally, i.e., in diet or as dietary supplements, while some are now present in many cosmetics, therefore the proposed study is of great practical significance [7].

When mice of Groups IV, V and VI treated topically with Aloe gel, orally with Aloe extract and both topically + orally with gel and Aloe extract two weeks before of DMBA/ croton oil application; body weight at different time period was measured to be increased as compared to group III (carcinogen control). The protection from body weight loss in Aloe treated group may be due to the presence of immuno stimulant compounds, micronutrients, minerals and essential amino acids etc in Aloe vera that makes healthy all the body systems and in turn increased the body weight of mice.

Aloe vera contains immuno-enhancing, anti-inflammatory, anti-neoplastic, anti- microbial and anti-oxidants compounds [10,

51, 31, 38, 26, 28, 21] that activate the immune system in order to induce apoptosis and suppress the proliferation and angiogenesis during the initiation and secondary modification stages of neoplastic development [50].

Tumor incidences were recorded as 100 per cent and the average number of tumor incidence was scored 3.6, whereas average latent period was recorded as 4.5 in weeks in mice belonging to group III (DMBA/carton oil treated).

Evidences have accumulated to suggest that it is perhaps due to reactive oxygen species (ROS) which play an important role in tumor initiation by enhancing or facilitating the metabolic activation and/or initiating effects of carcinogens [5] and induction of epidermal ornithine decarboxilase (ODC) [33].

Reactive oxygen and/or nitrogen oxide species–induced stress (RONOSS) and its downstream events are clearly important for carcinogenesis. RONOSS can be induced by exposure of carcinogenic xenobiotics and microorganisms [27] and the various cellular alterations induced by RONOSS play crucial role in carcinogenesis [37].The antioxidants are expected to inhibit RONOSS, because of an alteration in relevant enzyme profiles and quenching [36].

Tumor incidence, cumulative number of papillomas, tumor yield, tumor burden, tumor weight and tumor size were found to be decreased in all the experimental mice (groups IV, V & VI) but maximum reduction in all such parameters was evident in Aloe gel + Aloe extract treated mice (group IV).This fall may be due to factors such as inhibition of DMBA metabolism to its active form or delay in the promotion phase of tumorigenesis via down regulation in the production of ROS and inhibitory effects on tumor promoter-induced epidermal ODC activity [23].

Several studies have demonstrated direct inhibitory effects of AG on both tumor initiation and promotion. Kim and Lee [25] reported that polysaccharide fraction of Aloe inhibited cellular uptake of B(a) P resulted in inhibition of B(a) P DNA adduct formation. They also stated that Aloe, dose dependently increased the level of [3H] B (a) P in the subcellular medium, whereas the cellular concentration of [3H] B (a) P decreased. They further stated that treatment with Aloe resulted in statistically non significant induction of GST in liver and hence Aloe may enhance the elimination of benzopyrene metabolites by inducing detoxifying enzymes but cytochrome P-450 contents were not affected. Polysaccharides are given to cancer patients in consideration of their direct cytotoxic effects on cancer cells and direct improvements in immune surveillance [49].

Lipid peroxidase cause damage to cellular macromolecules by generation of reactive species and are considered to promote carcinogenesis [15].

In the present study, significantly lower the reduced glutathione (GSH), DNA, catalase, and protein activity was noted in the skin of carcinogen control mice (group III) as compared with Aloe treated experimental animals (groups IV, V, and VI) at the time of termination of the experiment (ie,16 weeks). A considerable elevation of LPO level was noted in the skin after DMBA and croton oil treatment, whereas administration of A vera (P [illegible].05) significantly reduced the level of LPO in all the Aloe treated experimental groups (IV, V, and VI) in comparison with the carcinogen control group.

Glutathione peroxidase activity, superoxide dismutase enxymes and phenolics anti-oxidants were present in A.vera gel, which may be responsible for these anti-oxidant effects [28, 8] indicated anti-tumor activity of A.vera gel in term of reduced tumor burden, tumor shrinkage, tumor nacrosis and prolonged survival rates. In addition to these effects, A. vera gel has also shown chemopreventive and anti- genotoxic effects of benzopyrene DNA adducts. Aloe vera is a good source of polysaccharides anti-oxidants and hence it is a good chemopreventive agent.

Lipid peroxidation (LPO) is a free radical chain reaction and mainly involves three distinct steps i.e. initiation, propagation and termination [30]. It results in a loss of biochemical and structural architecture of cellular organelles; therefore, it is a highly destructive process. Lipid peroxidation is initiated by hydroxyl radical (OH) which have sufficient energy and can abstract a hydrogen atom from methylene carbon of polyunsaturated fatty acid (PUFA) and initiate lipid peroxidation. Lipid radiolytic products such as alkozyl ($LO^\cdot$) and peroxyl ($LOO^\cdot$) radicals also initiate lipid peroxidation process by attacking on fresh lipid molecules [39]. The alkozyl and peroxyl can also attack on proteins and enzymes besides reinitiating lipid peroxidation.

The decreased lipid peroxidation which is measured by thiobarbituric acid reactive substances (TBARS) in the skin homogenate of Aloe treated mice is correlated well with the induction of antioxidants enzymes. Several low molecular weight compounds isolated from AG are capable of inhibiting the generation of reactive oxygen free radical and may protect tissues from excessive oxidative damage caused by free radicals.

Aloe gel is also rich in vitamin A (ß-carotene) C, E and B12, thiamine, niacin and folic acid, as well as minerals like sodium, potassium, zinc, chromium, selenium and iron [46, 6], Ascorbic acid (vitamin C) is effective water soluble and chain breaking antioxidant. It efficiently scavenges superoxide, hydrogen peroxide, the hydroxyl radical, peroxyl radicals, and singlet oxygen. Ascorbic acid protects membranes against peroxidative dames by trapping peroxyl radicals in the aqueous phase before they can initiate lipid peroxidation. It also has an indirect antioxidant action in that it can interact with the tocopherol radical to generate tocopherol (vitamin E) (another powerful antioxidant) [43].

Together with the retinoids, the selenium salts have been studied extensively as suppressing agents and have been found to experimental neoplastic system. Selenium can inhibit both the initiation and promotion phases of carcinogenesis; a continuous intake of selenium is necessary to achieve maximal inhibition of tumorigenesis [16].

Glutathione (GSH), a tripeptide of glutamic acid, cysteine and glycine, is the most abundant intracellular thiol compound present in virtually all mammalian tissues [44]. GSH is essential for protection of the cells against reactive oxygen species and free radicals produced even in normal metabolism [44]. By its multifunctional properties, GSH plays an important role in drug metabolism [19], radiation and cancer [45] immunology, aging and exercise [24].

Protection offered by Aloe vera to biochemical constituents against carcinogen in the present study can be attributed to an elevation in the glutathione level that could have been mediated through the modulation of cellular antioxidant level. Yagi [53] also reported that the aloesin derivatives of A. vera possess strong DPPH radical and superoxide anion scavenging activities and isolated a radical scavenging glycoprotein from A. vera gel that inhibits cyclooxygenase-2 (COX-2) and thromboxane A-2 synthatase enzyme activity at the promotion stage. A. vera reduces the risk of lipid peroxidation by the elevation in the level of skin GSH and catalase, thereby reduced the tumor incidence,cumulative number of papillomas, tumor burden and tumor yield. The onset of papillomas development being delayed when A.vera was administered at the different mode of treatment.

However, the greatest effects in the present study were achieved to the assumption that the plant extract may have either inhibited DMBAmetabolism to its active form, or delayed the promotion phase of carcinogenesis or down regulatd reactive oxygen species formation, by modulating ornithine decarboxylase, protein kinase C activity.

5. Conclusion

From the present study, it is evident that Aloe vera, the Indian medicinal plant, is a source of many anti-carcinogenic agents and antioxidants, which may be useful for the prevention of chemical induced skin cancer in mice. This work demands further study to evaluate the exact mechanism of chemoprevention offered by Aloe constituents as well as its possible chemopreventive efficacy against other types of tumors in various models.

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