IJPSR (2018), Volume 9, Issue 8 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 01 November, 2017; received in revised form, 30 January, 2018; accepted, 06 February, 2018; published 01 August, 2018

CHEMOPREVENTIVE ACTIVITY OF QUININE SULFATE IN DMBA-CROTON OIL INDUCED SKIN CARCINOMA IN MICE

Deepika Jhanwar and Jaimala Sharma *

Department of Zoology, University of Rajasthan, Jaipur - 302004, Rajasthan, India.

Keywords:

Skin cancer, Quinine sulphate, DMBA, Croton oil, Topical

Correspondence to Author:
Prof. Jaimala Sharma

Professor,
3A, Maharani's College,
Staff Quarter Near Diggi House,
Ram Singh Road, Jaipur - 302004,
Rajasthan, India.

E-mail: jaimalauor@gmail.com

ABSTRACT: Cancer has emerged as a major health problem globally as a consequence to the increased longevity of the population, changing environment and life style. Chemoprevention is a new and promising strategy for reducing cancer burden. The present study was conducted to evaluate the potential of Quinine sulphate to prevent chemically induced skin cancer in mice. Cancer was induced on 2-stage skin carcinogenesis model by single topical application of 7,12 dimethylbenz [a] anthracene (DMBA), as initiator, and two weeks later it was promoted by croton oil treatment thrice a week on the dorsal surface of mice for 16 weeks. Mice were divided into following groups: I Normal mice without any treatment, II Topical Acetone treated, III DMBA + Croton oil (Positive Control), Group IV Topical quinine sulfate treated (higher dose), Group V Topical quinine sulfate treated (lower dose). The differences in the values of the results of experimental groups were statistically analyzed which were significant in comparison to the control group. The animals of the quinine sulphate treated group had a significant reduction in tumor incidence, cumulative number of tumors, tumor yield and tumor burden when compared with the carcinogen-treated control animals. The average weight and diameter of tumors recorded were also comparatively lower in the quinine sulfate treated groups. Taken together, these findings indicate that quinine sulphate has the potential to become a pivotal chemopreventive agent that can reduce cancer.

INTRODUCTION: Non-communicable diseases including cancer are emerging as major public health problems in India. These diseases are lifestyle related, having a long latent period, needs specialized infrastructure and human resource for the treatment. Skin carcinogenesis is growing rapidly in the developed countries. Exposure to radiations, especially ultraviolet - B radiation is considered the principal cause for development of skin cancers due to the depletion of the ozone layer and changes in environmental composition [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(8).3454-62

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(8).3454-62

SCC accounts for 20 % of cutaneous malignancies and it is the second most common form of skin cancer. The incidence of cutaneous malignancies, including melanoma and non-melanoma skin cancer, is equivalent to the incidence of malignancies in all other organs combined [2]. The multistage skin carcinogenesis model is a widely acceptable model to test tumor development, DMBA is the most potent initiator that has ability to damage DNA and Croton oil is the most potent promoting agent [3].

Besides the traditional treatment methods like chemotherapy and radiotherapy, there should be an alternative preventive approach to reduce the cancer burden. Chemoprevention is regarded as one of the promising, efficient and relatively new strategy to prevent cancer. Administration of natural or synthetic compounds to prevent, slow

down, and reverse the occurrence of cancer is kept in category of chemoprevention [4]. The topical administration of anticancer drugs has been investigated specially in cases where the cancer has spread over large areas of the body. It is beneficial to increase patient compliance and to reduce surgical costs and undesirable scars [5].

Heterocycles seem to play an important role in biochemical reactions in cells' metabolism. Therefore, the use of synthetic cyclic compounds as anticancer drugs tries to mimic natural ligands and substrates in order to disturb the delicate balance in cells. Quinoline ring is one of the most commonly encountered aromatic heterocycles in medicinal chemistry and plays an important role in many biological systems [6] featuring Nitrogen atom as part of the ring system, with the chemical formula C_9H_7N. The quinoline and their derivatives have been extensively explored for their applications as anti filarial, anti-amoebic, antibacterial, anti-malerial, antifungal agents [7] and are useful in the treatment of tuberculosis, diabetes and convulsions [8].

A combination of artemisinin, which is a potent anti-malarial drug and aminolaevulinic acid, could kill colorectal cancer cells and suppress tumor growth effectively [9]. Looking towards the health benefits of quinine sulphate, the present experiment was conducted to evaluate possible anti-cancer activity of quinine sulphate against chemical induced skin carcinogenesis in mouse.

MATERIAL AND METHODS:

Experimental Animals: The random bred, 6-7 week old male Swiss albino mice of 25 ± 2 gm body weight were used in the study. Animals were bred and brought up in the well- ventilated animal house. The animals were housed in large spacious hygienic polypropylene cages under controlled conditions of temperature (25 ^{o}C ± 2 ^{o}C) and light (14 light: 10 dark). Saw dust (procured locally), was used as bedding material. The animals were fed standard mouse feed procured from Aashirwad Industries, Chandigarh (India), and tap water was given *ad libitum* to drink. Animal care and handling were done according to the guidelines set by the World Health Organization, Geneva (Switzerland).

Chemicals: For this study 7, 12-Dimethyl benzanthracene (DMBA) and croton oil were procured from Sigma Aldrich Co., St. Louise, USA. Quinine sulphate (Rez-Q) was purchased from Shreya life science Ltd., Roorkee (India). All Other chemical reagents and solvents used, were of highest purity and all were commercially available and of analytical grade.

Experimental Design: Animals for this experimental study were divided into the following groups having six mice in each group.

Group I: Normal mice without any treatment. Animals of this group did not receive any treatment.

Group II: Vehicle treated control. Acetone (100 µl/ mouse) was applied topically on the shaven dorsal skin in this group of mice and they were given double distilled water at the rate of 100 µl/ mouse/ day orally, thrice in a week for 16 weeks.

Group III: Carcinogen treated control. DMBA was applied topically over the shaven area of the skin of these mice with a single dose of 100 µg of DMBA in 100 µl of acetone. Croton oil (100 µl of 1% Croton oil in Acetone) was applied three times per week after two weeks later of DMBA application, until the end of the experiment (*i.e.* 16 weeks).

Group IV: Topical quinine sulfate treated. On the shaven area of dorsal skin of mice of this group QS was topically applied at the dose rate of 334 mg QS/100 gm vaseline.

Group IVa: (Experimental-1) QS was applied after an hour of Croton oil application during the experimental period, on the mice skin of this group.

Group IVb: (Control) QS was applied till the end of experiment, but DMBA and Croton oil were not used in this group of mice.

Group V: Topical quinine sulfate treated. On the shaven area of dorsal skin of mice of this group QS was topically applied at the dose rate of 167 mg QS/100 gm vaseline.

Group Va: (Experimental-2) QS was topically applied on the skin of mice of this group, after an hour of Croton oil application.

Group Vb: (Control) These mice were treated same as group Va, but without carcinogen.

Induction of Tumor: Carcinogenesis is a multi step procedure that continues through multiple noticeable stages, involving initiation, promotion and progression [10]. For the induction of skin Tumors, dorsal hair between the cervical and caudal portions of the animals were removed before 2 days to the initiation of the experiment, and 100 µL DMBA (100 µg/100 µL acetone) was applied. Two weeks after giving DMBA initiator, the Tumor promotion was started by the topical application of 100 µL Croton seed oil (1% v/v in Acetone), three times in a week, for the next 14 weeks.

Observations:

Body Weight: During the experimental period of 16 weeks, all mice were observed daily and body weight was taken weekly.

Organ Weight: Weight of liver, kidney, spleen and testis was taken after sacrifice.

Morphological Study: Tumors appearing on the shaven area of the skin were recorded at weekly intervals in all of the above groups. Only those Tumors that persisted at least for 2 weeks or with a diameter of more than 2 mm were taken into consideration for the final evaluation of the data. Skin Tumors, which were not seen after one observation, were not accounted.

(i) Tumor Burden: The average number of Tumors per Tumor bearing mouse was calculated.

(ii) Cumulative Number of Tumors: The total number of Tumors appeared till termination of the experiment, was recorded.

(iii) Tumor Yield: The average number of Tumors per mouse was estimated.

(iv) Tumor Incidence: The number of mice carrying at least one Tumor was expressed as percent incidence.

(v) Average Latent Period: The time lag between the application of the promoting agent and the appearance of 50 % of 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 Croton oil, and dividing the sum by the total number of Tumors.

$$\sum FX / N$$

Here F is the number of Tumors appearing each week, X is the number of weeks and N is the total number of Tumors.

(vi) Inhibition of Tumor Multiplicity: It was calculated by following formula-

Total number of Tumors in carcinogen treated control-Total number of Tumors in quinine sulfate treated group X100 / Total number of Tumors in carcinogen treated control

(vii) Tumor Weight: At the termination of experiment the weight of each Tumor was measured.

(viii) Tumor Diameter: The diameter of each Tumor was measured at end of the experiment.

RESULTS:

Body Weight: A gradual increase in body weight of mice was observed in the experimental groups, while the similar increase was not evident in carcinogen treated control animals (III).

Organ Weight:

(a) Liver Weight: Average liver weight of normal mice was compared with carcinogen treated (Positive control) group of mice. In normal and Acetone treated mice liver weight increase was 80.55% and 69.44% (I, II), respectively. When QS was applied topically with carcinogen on mouse skin, it increased by 61.11%, 59.25%, 37.96% and 43.51% in IVa, IVb, Va and Vb groups respectively. In comparison to carcinogen treated positive control group of mice significant increase was observed ($p<0.001$) in all the groups of mice.

(b) Kidney Weight: Average kidney weight was compared with carcinogen treated (Positive control) group of mice. In normal (group I) and Acetone treated (group II) mice increase in kidney weight was observed by 55.55% and 85.18%, respectively. When QS was applied topically on mouse skin it increased to 62.96%, 85.55%, 55.55% and 66.66%, in IVa, IVb, Va and Vb groups respectively. In comparison to carcinogen treated positive control group of mice significant increase was observed in kidney weight of normal mice ($p<0.001$).

(c) Spleen Weight: Average spleen weight was compared with carcinogen treated (Positive control) group of mice. In normal and acetone treated mice spleen weight decreased by 75 % and 78.5 % respectively. When QS was applied topically with carcinogen on mouse skin it decreased by 82.14 %, 78.57 %, 42.85 % and 42.85 % in IVa, IVb, Va and Vb groups respectively. Significant decrease was observed ($p<0.05$) in all the groups of mice, when compared with mice of carcinogen treated positive control group.

(d) Testis Weight: Average testis weight was compared with carcinogen treated (Positive control) group of mice. In normal and Acetone treated mice testis weight increase was observed to be 79.99 % and 40 % in I and II groups, respectively. When QS was applied topically with carcinogen on mouse skin it increased to 40%, 49.99%, 30% and 49.99% in IVa, IVb, Va and Vb groups respectively.

Morphological Parameters:

(a) Tumor Burden: In mice of carcinogen treated control group Tumor burden was 5 ± 0.56. When QS was applied topically it reduced to 4 ± 0.38 and 3.66 ± 0.45 in low dose treated and high dose treated mice, respectively.

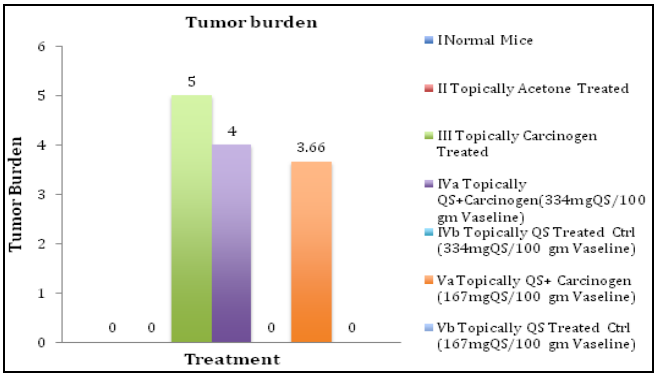

FIG. 1: TUMOR BURDEN

(b) Cumulative Number of Tumors: Carcinogen treated group had considerably higher tumor appearance at different weeks during the experiment as compared to Quinine sulfate treated. The cumulative number of tumors during the observation period in treated mice was less than the positive control (30) mice. In the topically QS applied mice cumulative number of tumors were quite similar in both the low and high dose treated mice that was 12 and 11, respectively.

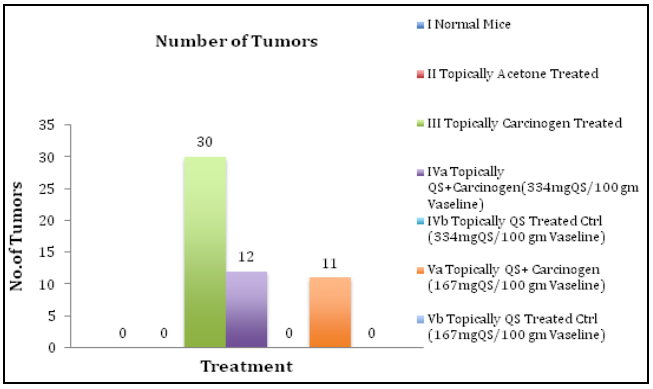

FIG. 2: CUMULATIVE NUMBER OF TUMORS

(c) Tumor Yield: In carcinogen treated (Positive control) group of mice tumor yield was 5 ± 0.50. When QS was applied topically with carcinogen on mouse skin it reduced to 2 ± 0.20 and 1.83 ± 0.21, in IVa and Va groups, respectively.

(d) Tumor Incidence: In the vehicle treated mice no tumor was observed. The incidence of tumor was 50% in mice of both the groups where QS was applied topically. The respective figure for carcinogen treated control was 100%. It means all the mice of this group had tumor on their skin.

(e) Average Latent Period: In both the groups of topically QS treated experimental mice IVa and Va, it was 12.54 and 12.25, respectively.

(f) Inhibition of Tumor Multiplicity: In mice treated topically with lower dose of QS it was 60.

(g) Tumor Weight: Total tumor weight was 1.31 gram in animals of positive control group. The total tumor weight declined in mice of topically QS applied groups to 0.346 gms and 0.271 gms in IVa and Va groups, respectively.

(h) Tumor Size: It was observed that mice having greater number of tumors also had greater number of large sized tumors.

In positive control mice 19 tumors were in the size range of 2 to 5 millimeter (mm) and 11 tumors were in size range of 6 to 9 mm. Mostly experimental mice had low number of tumors of big size range. Number of tumors was 9 and 9, in size range of 2 to 5 mm and 3 and 2 in size range of 6 to 9 mm, in animals of group IVa and Va, respectively.

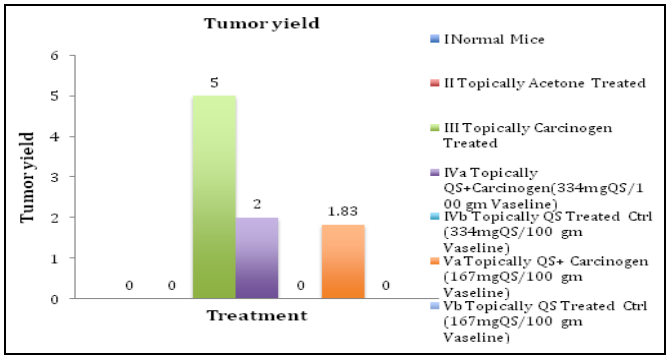

FIG. 3: TUMOR YIELD

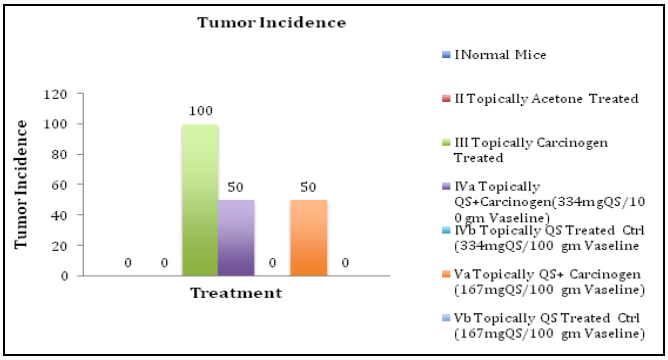

FIG. 4: TUMOR INCIDENCE

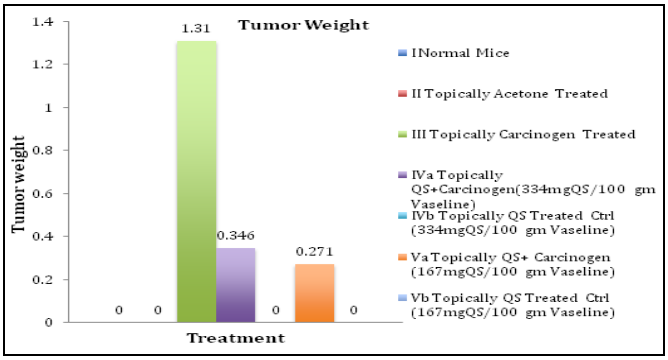

FIG. 5: TUMOR WEIGHT

TABLE 1: SHOWING TUMOR NUMBER, TUMOR WEIGHT AND TUMOR INCIDENCE

Treated Mice Group	Tumor number	Tumor weight	Tumor incidence
I Normal nice	0	-	0
II Topically acetone treated (Negative Control)	0	-	0
III Topically carcinogen treated (Positive Control)	30	1.31	100
IVa Topically QS + Carcinogen (334 mg QS/100 gm Vaseline)	12	0.346	50
IVb Topically QS Treated Ctrl (334 mg QS/100 gm Vaseline	0	0	0
Va Topically QS + Carcinogen (167 mg QS/100 gm Vaseline)	11	0.271	50
Vb Topically QS Treated Ctrl (167 mg QS/100 gm Vaseline)	0	0	0

TABLE 2: TUMOR INHIBITORY MULTIPLICITY AND TUMOR SIZE

Treated mice group	Tumor inhibitory multiplicity	Tumor size	
		2-5 mm	6-9 mm
I Normal Mice	0	-	-
II Topically acetone treated (Negative Control)	0	-	-
III Topically carcinogen treated (Positive Control)	0	19	11
IVa Topically QS + Carcinogen (334 mg QS/100 gm Vaseline)	60	9	3
IVb Topically QS Treated Ctrl (334 mg QS/100 gm Vaseline)	0	-	-
Va Topically QS+ Carcinogen (167 mg QS/100 gm Vaseline)	63.33	9	2
Vb Topically QS Treated Ctrl (167 mg QS/100 gm Vaseline)	0	-	-

TABLE 3: TUMOR BURDEN, AVERAGE LATENT PERIOD AND TUMOR YIELD

Treated mice group	Tumor burden	Average latent period	Tumor yield
I Normal mice	0	-	-
II Topically acetone treated (Negative Control)	0	-	-
III Topically carcinogen treated (Positive Control)	5 ± 0.56	0	5 ± 0.50
IVa Topically QS + Carcinogen (334 mg QS/100 gm Vaseline)	4 ± 0.38	12.25	2 ± 0.20
IVb Topically QS Treated Ctrl (334 mg QS/100 gm Vaseline)	0	-	-
Va Topically QS + Carcinogen (167 mg QS/100 gm Vaseline)	3.66 ± 0.45	12.54	1.83 ± 0.21
Vb Topically QS Treated Ctrl (167 mg QS/100 gm Vaseline)	0	-	-

DISCUSSION: In a normal cell an unvarying life cycle and reproduction is followed. Cancer cells are anomalous or mutant cells. This occurs when certain cell DNA catches an altered signal that

leads to mutation. In normal condition when cell senses a mistake it destructs itself or it is removed from the body. Cancer is the outcome of a series of molecular events that basically change the common properties of cells. In cancer cells the normal control systems that check cell overgrowth and the attack of other tissues are restricted. These transformed cells divide and grow in the presence of signals that usually prevent cell growth; consequently, they no longer need special signals for inducing cell growth and division.

NMSCs (Nonmelanoma skin cancers) present many changes, at both the gene and the chromosome levels. Breaks in the structure of the DNA molecule are responsible for characteristic chromosomal aberrations in skin tumors. It has been demonstrated that the combination of certain polymorphisms raises the risk of evolving SCC (Squamous cell carcinoma). Development of SCC is also related to over-expression of Ras (signal transmitter). The over-expression of anti- apoptotic proteins which, belong to the Bcl-2 family protein; Bcl-xL is a crucial activator for skin carcinogenesis and McI-1, that is an indispensable survival factor for keratinocytes, is seen in SCCs.

Carcinogenesis is a multistep procedure that continues through multiple noticeable stages, involving initiation, promotion and progression. DMBA initiates tumorigenesis and the croton oil promotes development of the visible tumor stage. Carcinogens can cause cancer either by direct action in the cellular DNA or through mechanisms that produce chemical species (such as free radicals, reactive oxygen species, carcinogenic metabolites *etc*.), which enter the cell nucleolus leading to mutations in cellular DNA. Formation of stable DMBA-DNA adducts can cause activation of proto- oncogene or can inactivate tumor suppressor genes during tumor initiation. Mutation of c-Harvey (Ha)-ras oncogene is supposed to involve in tumor initiation in mouse skin after DMBA treatment [11].

Skin cells are continuously exposed to ROS and oxidative stress from exogenous and endogenous sources. ROS may act on pyrimidines, purines and chromatin proteins, which, lead to base modifications, DNA adduction and gene mutation and may be helpful in carcinogenesis [12]. A gradual increase in body weight of mice was observed in the normal and all the experimental mice while the similar increase was not evident in carcinogen treated control animals. In carcinogen treated positive control group of mice 30 tumors were observed. Number of tumors in other groups of mice were, 12 and 11, in IVa and Va, groups, respectively. In comparison to carcinogen treated control group tumor yield was lesser in other groups. Tumor burden was lesser in all the topically quinine sulfate applied experimental mice, when compared to positive control group of mice.100% tumor incidence was observed in mice of group III and decreased tumor incidence was observed in mice of other experimental groups. Average latent period was the highest in Va group. Total tumor weight was quite low in all the other experimental groups as compared to positive control mice. Lowest tumor weight was observed in Va group. Carcinogen treated positive control mice exhibited higher number of large sized tumors.

The general health or body status of the experimental animals is one of the important parameters. Monitoring of body weight is essential during the tumorigenesis protocol because it gives an indication of the general health of the experimental animals. Among the different indicators used for identifying general health status, the body weight is one of the visible indicators.

There are several causes of weight loss. Cancer itself, because in an effort to fight the cancer, the body produces cytokines, which can lead to weight loss, muscle loss and a decrease in appetite. It was found that MIC-1(Macrophage Inhibitory Cytokine -1) was at very high level in the mice with prostate cancer and when antibodies were given to this cytokine the mice didn't lose any weight. So it looks like it's the immune system, trying to respond to the cancer [13].

Cancerous tumors are not foreign objects in the body they are made up of the same DNA of the person, hence the body feeds and nourishes the tumor and helps it to grow like any other body part. The body channelizes all the energy to the rapidly growing tumor. This is one of the reasons of loss in body weight.

In the present study a decrease in body weight was observed in DMBA-TPA treated group when

compared to their initial body weight. The decrease in body weight after treatment with DMBA might be due to suppression of food and water intake. Similar results were reported on the body weight in the conditions of DMBA induced squamous cell carcinoma of skin. At the end of the treatment period, it was observed that mice in control and Quinine sulfate treated groups gained weight when compared to their initial body weight. Further, the increase in the body weight in the carcinogen treated mice along with quinine sulfate revealed that cancer prevention involves pharmacological intervention with these substances to prevent or inhibit or reverse the process of carcinogenesis or prevent the development of cancer [14]. The role played by liver in the removal of substances from the portal circulation makes it susceptible to first and persistent attack by offending agents like viruses, chemicals, toxins in food, peroxides, drugs, environmental pollutants *etc*.

The pharmacological effects of topical substances directly depend on micro vascular parameters like blood flow rate. The skin holds a rich vascular network system that controls and deals several actions in the skin. Three types of capillaries are found in the human body. The capillaries are most important in relation to the clearance because it is the first permeable part of circulation encountered by a topically applied permeant [15].

The bioavailability of quinine sulfate is 76-80% in healthy adults. quinine sulfate is metabolized by oxidation of the quinoline or the quinuclidine moieties into four primary metabolites. 3-hydroxy-quinine, 2'quinone, demethylquinine and 10, 11 dihydroxy quinine and at least 11 secondary metabolites. Cytochrome P4503A catalyses the formation of 3-OH-quinine [16]. Quinine sulfate is metabolized mainly by CYP3A4 and some role of CYP1A2 and CYP2C8 have been proposed. Quinine sulfate may inhibit the metabolism of certain drugs that are CYP3A4 substrates.

Different Quinoline derivatives have displayed cytotoxicity towards cancer cells. Some derivatives of Quinoline have exhibited anti-inflammatory and apoptosis inducing activities by inhibiting cyclo-oxygenase enzyme. With morphological study chemopreventive activity of quinine sulfate was displayed which might be due to its cytotoxic and anti-inflammatory properties. Recent studies found that numerous quinoline derivatives display potent anti-cancer activity by targeting different cellular pathways, including multidrug resistance, proliferation and apoptosis. These compounds show effect by activating or inhibiting certain cell processes [17]. So far, numerous quinoline derivatives, both in natural and synthetic products, have been reported to possess anticancer activities through induction of different pathways of apoptosis [17].

The ligation of (Toll-like receptor) TLR7 and TLR 8 trigger inflammatory responses. Imiquimod is an imidazoquinolin, which is used for the treatment of some forms of skin cancer and it has been characterized as a specific agonist of Toll-like receptor 7 (TLR7) and 8 (TLR 8) and successively, activation of nuclear factor-kappa B (NF-kappa-B). This activity leads to the induction of pro-inflammatory cytokines like interferon-α (IFN-α), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), chemokines and other mediators causing activation of antigen-presenting cells and other components of innate immunity and finally, mounting of a profound T-helper (Th1)-weighted antitumoral cellular immune response. Several quinolines work by binding to DNA with high affinity, inhibiting DNA topoisomerases I/II and displaying cytotoxic and antitumor activities [18].

Cell cycle arrest in G0/G1 phase and significant decrease in G1/S phase was observed in Quinine treated cells. It was suggested that the use of Quinine causes the cells to undergo DNA fragmentation, it is more potent to inhibit the cell proliferation and caused cytotoxicity [19]. Several Quinoline compounds display their anticancer activity through cell cycle arrest, particular mechanisms include; apoptosis, angiogenesis inhibition, inhibition of receptor and DNA. Intercalation is noted in some quinoline derivatives

Cyclo-oxygenases (COXs) are used as rate-limiting enzymes in arachidonic acid metabolism and prostaglandin production. COX-2 is involved in skin inflammation and apoptosis. The topical Diclofenac works as a nonspecific COX inhibitor and is effective and well tolerated for the treatment of actinic keratosis, which is precursor of cutaneous squamous cell carcinoma. In animal models, oral

and topical COX-2 inhibitors have displayed chemopreventive activity against chemically and UV light - induced skin cancers [20]. Some quinoline derivatives display cyclooxygenase inhibiting activity.

With this study it can be proposed that quinine sulfate play important role in the activation of caspases, growth inhibition, arresting the cell cycle at the G1, S or G2/M phase and then inducing apoptotic cell death. It might be useful in displaying cytotoxicity by helping the cells to undergo DNA fragmentation and binding to DNA with high affinity, intercalating between double stranded DNA, inhibiting DNA topoisomerases I/II and working as COX inhibitor. It might be useful in stimulating innate immunity and its components by showing agonistic activity towards toll-like receptors 7 and 8 and to the induction of pro-inflammatory cytokines causing activation of antigen-presenting cells. The precise mechanism of action of quinine sulfate can be postulated, on the basis of the results obtained from the previous and current studies, it is suggested that quinine sulfate scavenges the free radicals to reduce the oxidative stress and simultaneously regulate various signaling pathways which are responsible for cell proliferation and apoptosis. So quinine sulfate treatment may be a possible therapeutic approach for cancer.

Quinine sulfate inhibits nucleic acid and protein synthesis. It also stimulates release of insulin and increases energy consumption. So availability of important biomolecules in the tumors is reduced which may help in cancer prevention. The exact mechanism of action of this treatment is not clear but probable mechanisms of chemopreventive effect might be apoptosis, maintaining oxidative stress, anti inflammation, anti-proliferation, anti-lipid peroxidation, cytototoxicity and genotoxicity.

CONCLUSION: Quinine sulfate might have worked here by inhibiting COX-2 enzyme, as topoisomerase inhibitor, inducing interferon-α, DNA intercalative property or might have started some other cytotoxic mechanism. The chemo-preventive efficacy of quinine sulfate in this study suggests its potential role as an anticancer agent.

ACKNOWLEDGEMENT: We acknowledge financial support-from UGC in the form of UPE Non NET scholarship to Deepika Jhanwar.

CONFLICT OF INTEREST: There is no conflict of interest.

REFERENCES:

1. George VC, Vijesh VV, Dehigaspege AI, Lakshmi CA, Anbarasu K, Kumar DR, Ethiraj R, Kumar RA and Rupasinghe HP: Mechanism of action of flavonoids in prevention of inflammation-associated skin cancer. Curr Med Chem 2016; 23(42): 1-20.
2. Santosh K, Katiyar HC and Pal RP: Dietary pro-anthocyanidins prevent ultraviolet radiation-induced non-melanoma skin cancer through enhanced repair of damaged DNA-dependent activation of immune sensitivity. https://doi.org/10.1016/j.semcancer. 2017.04. 003
3. Das MK and Bharali R: Chemopreventive potential of Diosgenin against 7, 12-Dimethylbenz (a) anthracene (DMBA) induced skin carcinogenesis in mice. International Journal of Medicine and Pharmaceutical Sciences 2014; 4(1): 49-58.
4. Albini A, Decensi A, Cavalli F and Costa A: Cancer prevention and interception: A new era for chemo-preventive approaches. Clin Cancer Res 2016; 22(17): 4322-4327.
5. Uchechi O, John DNO and Attama AA: Nanotechnology and Nanomaterials » "Application of Nanotechnology in Drug Delivery", Demir Sezer (editor).Chapter 6. Published under CC BY 3.0 license by INTECH publication, 2014.
6. Wahab BFA and Khidre RE: 2-Chloroquinoline-3-carbaldehyde II: synthesis, reactions and applications. Journal of Chemistry 2013; 2013: 1-13.
7. Gomez CMM and Kouznetsov VV: Recent developments on antimicrobial quinoline chemistry. Microbial pathogens and strategies for combating them: science, technology and education. A. Mendez-Vilas (Editor) Published by Formatex Research Center 2013; 666-677.
8. Boopathi M, Udhayakala P, Ramkumaar GR and Renuga TS: Spectroscopic characterization and DFT exploration of 2-(4-methoxybenzyloxy)-4- methylquinoline. Der Pharma Chemica 2016; 8(15): 187-197.
9. Jigang W, Jianbin Z, Yin S, Chengchao X, Chongjing Z, Yin KW, Yew ML, Sanjeev K, Yingke H, Teck KL, Weiying S, ZiChun H, Han Ming S and Qingsong L: Mechanistic investigation of the specific anticancer property of artemisinin and its combination with aminolevulinic acid for enhanced anticolorectal cancer activity. ACS Central Science 2017; 3(7): 743.
10. Vanitha MK, Baskaran K, Periyasamy K, Saravanan D, Ilakkia A, Nithya G, Selvaraj S, Kasthuri D, Sakthisekaran D and Anandakumar P: 7, 12-Dimethyl benz[a]anthracene (DMBA) induced carcinogenesis - an overview. Adv J Pharm Lif Sci Res. 2015; 3(1): 7-24.
11. Saha D and Hait M: An ontological design: Two stage mouse skin carcinogenesis induced by DMBA and promoted by Croton oil. Asian J Res Pharm Sci 2012; 2: 1-3.
12. Sullivan LB and Chandel NS: Mitochondrial reactive oxygen species and cancer. Cancer and Metabolism 2014; 2(17): 2049-3002.
13. Chris: Why do cancer and AIDS patients lose weight so rapidly? The Naked Scientists: Science Questions; 2009.
14. Chinchali JF, Sanakal RD and Kaliwal BB: Effect of *Clerodendrum serratum* leaf extract on biochemical and oxidative stress parameters of testis in 7, 12-Dimethylbenz

[a] anthracene induced skin carcinogenesis in swiss albino mice. Recent Research in Science and Technology 2012; 4(7): 8-15.

15. Nair A, Jacob S, Aldhubiab IB, Attimarad M and Harsha S: Basic considerations in the dermatokinetics of topical formulations. Braz. J. Pharm. Science 2013; 49(3): 423-434.
16. Roy L, Leblanc M, Bannon P and Villeneuve JP: Quinine pharmacokinetics in chronic haemo dialysis patients.Br J Clin Pharmacol2002; 54(6): 604-609.
    Ding Y and Nguyen TA: PQ1, a quinoline derivative, induces apoptosis in T47D breast cancer cells through activation of caspase-8 and caspase-9. Apoptosis 2013; 18(9): 1071-1082.
17. Lin YH, Yang SH, Chien CM, Hu XW, Huang YH, Lu CM, Chen YL and Lin SR: Induction of G2/M phase arrest and apoptosis by a novel indoloquinoline derivative, IQDMA, in K562 cells. Drug Dev Res 2006; 67: 743-751.
18. Krishnaveni M and Suresh K: Induction of apoptosis by Quinine in human laryngeal carcinoma cell line (KB). Int J Curr Res Aca Rev 2015; 3(3): 169-178.
19. Zhan H and Zheng H: The role of topical cyclooxygenase-2 inhibitors in skin cancer: treatment and prevention. Am J Clin Dermatol 2007; 8(4): 195-200.

How to cite this article:
Jhanwar D and Sharma J: Chemopreventive activity of quinine sulfate in DMBA-croton oil induced skin carcinoma in mice. Int J Pharm Sci & Res 2018; 9(8): 3454-62. doi: 10.13040/IJPSR.0975-8232.9(8).3454-62.