

Recent Advancements in Treatment of Skin Cancers Induced by UV Rays and DMBA /Croton Oil.

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Abstract

Cancer is a crucial epidemiological health issue; it is the second-highest root for death in both males and females in developed as well as in developing countries. The surface epithelium of skin is in long term disclosed to a large number of atmospheric toxins, including tobacco smoke, providing exposed individuals at hazardous risk of developing cancer. Apart from ultraviolet radiation (UVR), other familiar risk factors of skin cancers include occupational and environmental exposures to polycyclic aromatic hydrocarbons, arsenic, and ionizing radiation. Under such circumstances, chemoprevention is one of the best procedures to prevent cancer development. A considerably convincing effective compound with slight toxicity can be more practical than a formidable chemo preventive agent with excessive toxicity for people those are at hazard of cancer. Above 50% of obtainable anticancer drugs on the market are acquired from natural sources, of which above 70% of anti-cancer agents meet their inception in natural sources. These natural sources cover plants, animals, microbes and marine life, Anti-Cancer Dietary Components, Phytochemicals and Nutraceuticals. This present review mainly goals at providing an outline of anti-cancer composites, those derived from natural sources, that are presently used in carcinoma chemotherapies, or those which has been described and reported to show anti-melanoma, or anti-skin cancer activities. The natural compounds demonstrated in this review article comprises of Marine Sources, Microbial Sources, Plant Sources, Anticancer dietary compounds, Phytochemicals and Nutraceuticals.

Keywords

Skin Cancer; Tumor; Marine; Microbial; Plant; Phytochemicals; Nutraceuticals.

Introduction

Cancer is one of the dominant public health issues, being the second-highest issue, it gives rise to death in both men and women in developed as well as in developing countries. Environmental contamination is one of the chief components in the development of cancer. The surface epithelium is severely disclosed to a vast number of atmospheric toxins, including tobacco smoke, making exposed individuals at excessive risk of developing cancer. Under such circumstances, chemoprevention is one of the finest plans of action to obstruct cancer development. Chemoprevention is the one that puts in touch with the use of synthetic chemicals or natural products that aid in cancer prevention. A huge number of compounds have been tested

for the interception of cancer; however, during the estimation of a chemo preventive compounds not only its advantageous effects, but also the toxicity must be taken into attention. A powerful and effectual compound with little toxicity can be more convenient than a formidable chemo preventive agent with high toxicity for individuals who are at the hazard of cancer. Abundantly occurring antioxidants such as vitamins, nutrients, and other plant products are innocuous or markedly harmless than the synthetic chemo preventive agents, and some are the ancient constituents of the human diet. Epidemiological and investigational studies have contributed with particulars about potential antioxidants present in dietary components such as cereal crops, fruits and vegetables that are noted to inhibit numerous cancers at distinct stages, particularly skin cancer^[1]. Michael Sporn first coined the term “chemoprevention” in 1976, which now on the whole include to the use of therapeutic or natural agents to forbid the initiation, promotion, and progression of carcinogenesis . Since then, chemoprevention has endured a scope of active study and exploration particularly with regards to the intervention of human cancer^[2]. Human cancer endures an origin of high unwholesomeness and mortality around the globe. Chemotherapy is a particular major perspective to treat cancer by conveying a cytotoxic agent to the cancer cells. Despite the fact a growing number of studies for the therapies of cancer have progressed recently, these have collapsed to catch up with the extending resistance to anti-cancer drugs in cancer cells as well as to the associated side effects of conventional cancer chemotherapy. For that reason, progression of a novel class of anti-cancer drugs that dearth the toxicity of chemotherapeutic agents and are unaltered by familiar mechanisms of chemoresistance would be a major evolution in cancer treatment. In these circumstances, the development of antimicrobial peptides (AMPs) and anti-cancer peptides (ACPs) is presently being proposed to be an engrossing and hopeful alternative. Though these AMPs have fundamentally been read up and developed as practicable alternatives for encountering infectious diseases, their use as anti-cancer peptides (ACPs) in cancer therapy either alone or in combination with other conventional drugs has been considered as a therapeutic master plan which yet remains to be investigated and researched. furthermore, it has also been recommended that anti-cancer effectuality of drugs can be strengthened by consignment of multifunctional agents to achieve collective effects and subdue drug resistance^[3].

In recent times, it has been a developing awareness in the recognition of naturally occurring dietary factors as possible anticarcinogens. Since the human diet contains a variety of mutagens, carcinogens, antimutagens, and anticarcinogens, it is becoming gradually and progressively clear that dietary practice may play a prime role in possibility of emerging a number of major human cancers. For example, epidemic proof suggests that the high consumption of green or yellow vegetables in diet is linked with a lower risk for cancer at various sites. It is therefore been believed that the identification of these dietary antimutagens and anticarcinogens may furnish an empirical approach for the chemoprevention of cancer^[4]. Non-melanoma skin cancer (NMSC) is comprised of two types squamous cell carcinoma (SCC) and basal cell carcinoma. Globally Basal Cell Carcinoma constitutes nearly 80% and Squamous Cell Carcinoma

constitutes nearly 20%. According earlier conducted reports, SCC has a higher prevalence in comparison to BCC^[5].

Apart from ultraviolet radiation (UVR), other additional risk factors of NMSC is comprised of occupational and environmental subjection to polycyclic aromatic hydrocarbons, arsenic, and ionizing radiation. Polycyclic aromatic hydrocarbons arise during the incomplete flaming of organic materials, including wood, petroleum and coal, and are well known for their noxious possibilities aside from being carcinogenic and mutagenic in nature. 7,12-Dimethylbenz(a)anthracene (DMBA) is the greatest common polycyclic aromatic hydrocarbon used as an initiating agent in chemically provoked skin cancer models, and 12-O-tetradecanoylphorbol-13-acetate (TPA), Croton oil is a tumor promoter urging two-stage skin cancer model, it has been elucidated to closely mimic human SCC. In general, skin carcinogenesis is known as a multistage course of action, which comprises of initiation, acceleration, development and progression. Recognition of successful chemoprevention agents gives the impression to be one of the most achievable art of war to overrule or obstruct carcinogenesis^[5].

Pathophysiology

Ultraviolet radiation penetrates into the basal layer of epidermis (10% of the surface) and directly induces DNA damage, like cyclobutene type pyrimidine dimers and photoproducts which cause mutations at the other sites of the DNA damages. Further, UVB and UVA radiations are demonstrated to supply reactive oxygen species (ROS) within the cells and skin which cause DNA damage resulting in point mutation and abnormal cell proliferation. additionally, to those tumor initiating effects, UV radiation also activates variety of transcription factors which induce the upregulation of genes involved in cell proliferation and performance. ROS can induce activation of the activator protein-1 transcription factor (AP-1) which can play a crucial role in tumor promotion^[6]. 7,12 Dimethyl Benz[a]anthracene (DMBA) may be a prototypical polycyclic hydrocarbon, a serious class of environmental carcinogen that has been employed to promote tumors in laboratory animals. Mammary and skin tumors are often produced in mice following administration of DMBA that causes upregulation of the cellular cytosolic receptor, the Aryl hydrocarbon receptor. Upon ligand activation, the Aryl hydrocarbon receptor trans locates into the nucleus and associates with the co-factor Aryl nuclear translation protein to induce CYP1A1, CYP1A2 and CYP1B1 genes there is growing evidence that Aryl hydrocarbon receptor also regulates various down-stream proteins including proliferating cell nuclear antigen (PCNA). Further, other mechanisms like generation of reactive oxygen species and nuclear factor κ B (NF- κ B) also are important controlling factors in proliferation and branching. Thus, due to the central role of Aryl hydrocarbon receptor and PCNA in

many xenobiotics related toxicity and carcinogenesis, the look for chemical inhibitors of Aryl hydrocarbon receptor and PCNA has assumed importance in chemoprevention. Several pathways are known to be mediated through p53-induced apoptosis and one among these involves the Bcl-2 and Bax proteins. The Bcl-2 family consists of both pro-apoptotic and anti-apoptotic members that elicit opposing effect on mitochondria. Bax promotes release of cytochrome into the cytosol from mitochondria that activates Caspase-3, which executes apoptosis via the activation of Caspase-9. Anti-apoptotic proteins like Bcl-2 and Bcl-xL, which are transcriptionally suppressed by p53, preserve the integrity of mitochondria that blocks the discharge of cytochrome preventing apoptosis [7].

Recent Advancements made in Skin cancer treatment:

Natural Sources of Anti-Cancer Compounds

A bounty of natural assets for therapeutic use persist globally, of which numerous assets have not yet been utilized for achievable implementation in the pharmaceutical industry. above 50% of all obtainable drugs on the market are obtained from natural sources, of which above 70% of anti-cancer agents own their inception in genuine natural sources. These genuine natural sources cover plants, animals, microbes and marine life. Plants are one of the extremely utilized natural resource for therapeutic uses in the pharmaceutical science and still contain as the leading natural source for novel drugs and lead compounds, due to their availability and abundance. To date, only some naturally derived drugs exist on the market that goal skin related cancers, considering that none have yet been officially agreed for topical application. This could be ascribed to the known after effects of these agents when topically applied to the skin. The following segments offer an outline of compounds from different natural sources that have been found to show activity against different types of cancer, with a specific focus on melanoma.

1. Marine Sources

In the past few years, attentiveness in the prospective of marine fauna and flora as an origin of novel medicinal agents has grown remarkably. Substantive investigation, aimed at using this vast natural resource is being carried out globally. The high anti-tumor effectiveness of agents, determined from marine resources, speculates the high prospective of the ocean as a possible origin of anti-cancer drugs. Extracts from sponges, algae and marine cyanobacteria have shown the strong powerful anti-cancer activities. Laminarins, fucoidans, alginic acids and carrageenan are few of the compounds isolated from marine sources that have been found to reveal effective anti-cancer activities. Though numerous anti-cancer compounds from marine origin have been isolated and certified in vitro and in vivo and taken through different stages of clinical testing, only four anti-cancer drugs of marine origin have attained to the market so far. These anti-cancer drugs are cytarabine, trabectedin, denibulin mesylate and brentuximab vedotin,

derived from *Cryptotethia crypta*, *Ecteinascidia turbinata*, *Halichondria okadai* and *Symploca hydnoidea*, respectively. Cytarabine is a pro-apoptotic compound that also acts by inhibiting cell growth in cancerous cells. In 1998, the Food and Drug Administration (FDA) had acknowledged the first marine derived compound, cytarabine, for clinical use as an anti-cancer agent in the treatment of acute myelogenous leukemia. Trabectedin, a derivative of Caribbean tunicate, was next validated for treatment of metastatic soft tissue carcinoma in 2007 by the European Commission. In 2009, trabectedin received even further approval for the treatment of relapsed, platinum sensitive ovarian cancer. Eribulin mesylate was then accepted as true by the FDA for clinical use as part of a third line treatment regimen for advanced, metastatic breast cancer in 2010. Brentuximab vedotin received FDA approval for treatment of systemic, anaplastic, large cell lymphoma and Hodgkin's lymphoma in 2011. These four anti-cancer drugs have been further put through to the various stages of clinical trials for their possible use in more diverse types of cancer, either alone or as part of a treatment regimen. Aplidin, bryostatin-1, salinosporamide and zalypsis are other examples of marine-derived compounds that are currently undergoing clinical trials for potential use as anti-cancer drugs. Many more marine derived compounds with anti-cancer potential are presently undergoing pre-clinical investigation.

2. Microbial Sources

The malignancy regression activity of bacteria was discovered and applied clinically over a century ago, when Coley observed that tumors in patients that had been fortuitously infected with *Streptococcus pyogenes* had degenerated. Such regression was due to an immune response stimulated by the bacterial infection and it was this discovery that gave rise to the arrival of cancer immunotherapy. Ever since, much research has been done on microbes to study their anti-neoplastic potential. The chemical diversity and approachability of microbes with respect to collection, culturing and fermentation make them an extremely applicable source of pharmaceutically active compounds. Anthracyclines, bleomycin, staurosporins and actinomycin are groups of microbially derived anti-cancer compounds in clinical use

Whole bacteria can be used in their live, attenuated, or genetically modified forms to stimulate immune responses, but this may potentially consequence in side effects that can be eluded by using bacterially derived products instead. Toxins from microorganisms can have superior effects in humans, such as rapidly end the existence of dividing cells in tumors.

3. Plant Sources

The vinca alkaloids, including vincristine, vinblastine and vinorelbine, were the earliest plant-derived anti-cancer agents to obtain acceptance for clinical use. Subsequently came the discovery and acceptance of the podophyllotoxin derivatives (i.e., etoposide and teniposide), taxanes (i.e., paclitaxel and docetaxel) and camptothecin derivatives (i.e., irinotecan and topotecan). The mechanism of action of the vinca alkaloids includes interaction with tubulin so as to interrupt the assembly of the mitotic spindle, which in turn leads

to the demise of actively dividing cells. Clashing to the vinca alkaloids, taxanes work by balancing the microtubule, instead of destabilizing it. The stabilization of the microtubule consequences in an imbalance between tubulin and microtubules, which affects normal cellular function and in turn outcomes in cell death. Camptothecins and podophyllotoxins inhibit topoisomerase I through various mechanisms, but both cause disordering of the cell division action.

Berberine, a naturally occurring isoquinolone alkaloid was tested in combination with doxorubicin on human melanoma cells and in vivo on mice. It was found that this mixture had suppressed tumor growth in vitro and in vivo. Extracts of *Tilia amurensis* and *Camellia sinensis* were tested on cancer cell lines beginning from the skin and they were found to have cytotoxic effects in vitro. It is further notified that some phytochemicals, such as epigallocatechin-3-gallate and apigenin have revealed a higher inclination for cytotoxicity towards melanoma and epidermoid carcinoma cells, contrasted to normal cells and such chemicals are increasingly being explored.

4. Anti-Cancer Dietary Components and Phytochemicals

Phytochemicals possessing anti-inflammatory, immuno-modulatory and anti-oxidant properties, generally have the highest possibility of displaying chemo-preventive behavior in skin cancers. Several attempts have been made to discover the connection between antioxidant properties of phytochemicals and their anti-cancer potential. Although no solid proof of such a connection has been found yet, the anti-oxidant activity of a phytochemical is being considered as a sign of potential anti-cancer activity. Carotenoids, flavonoids and terpenoids are few groups of phytochemicals with high anti-cancer potential ^[8].

Phytochemicals are biologically active compounds that may have possibility in health welfare, especially in the chemoprevention of cancer. Many phytochemicals have polyphenol groups comprising of multiple hydrophilic hydroxyl groups which act as scavengers for free radicals and reactive oxygen species (ROS), thereby keeping the cells secure from oxidative damage on DNA, protein, and lipids. Phytochemicals have the potential to play a separate role in skin cancer. First, pre-cancerous and cancerous skin lesions are readily attainable to both the subject and physician. This is advantageous to the development of topical agents that can be applied only to the suspicious malignant area of change with minimal damage to normal skin. Several favorable phytochemicals have been discovered in a range of fresh fruits, vegetables, roots, and herbs, such as epigallocatechin-3-gallate, resveratrol, curcumin, proanthocyanins, silymarin, apigenin, capsaicin, genistein, indole-3-carbinol, and luteolin; these have been studied and reasoned to improve cancer chemoprevention and treatment^[2].

5. Nutraceuticals for Skin Cancer Patients

The word “nutraceuticals” was coined in 1989 by Stephen L. DE Felice, MD, an American medical doctor. A nutraceutical is any food-derived supplement that has a medical benefit in stopping illness and promoting health. Nutraceuticals often can be used replaceable with terms such as dietary supplements, dietary ingredients, or functional food. Although, dietary supplements may not necessarily be derived from foods, nutraceuticals, on the other hand, are entirely derived from foods. Thus, nutraceuticals are natural bioactive products that have good curative properties for treatment of broad range of diseases. With the raise in skin cancer rates plus mounting health care costs, there is an increased aspiration to nurture a healthy lifestyle. Hence, to promote quality of life, scientists are highlighting their interests on the role of diet and nutrition in disease prevention.

List of Spices;

Turmeric (Curcumin)

Ginger (Gingerols, shogaols)

Cloves (Eugenol)

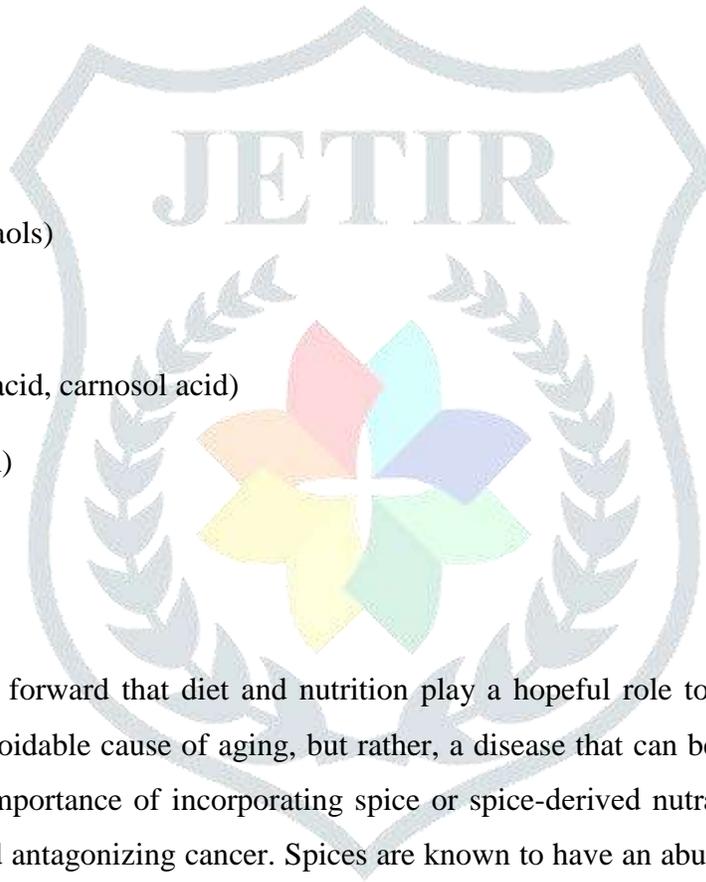
Rosemary (Rosmarinus acid, carnosol acid)

Saffron (Crocic acid, crocetin)

Capsaicin (Capsaicin)

Garlic (Allicin)

Mounting proof has put forward that diet and nutrition play a hopeful role to the fight against cancer. Cancers are not an unavoidable cause of aging, but rather, a disease that can be curable, largely through lifestyle changes. The importance of incorporating spice or spice-derived nutraceuticals in one’s diet is obliging in opposing and antagonizing cancer. Spices are known to have an abundance of health gain and benefits. countless studies have recorded the anti-inflammatory, antiproliferation, antimicrobial, and antioxidant properties of spices. Since oxidative stress, inflammatory stress, and immune system stress have been related with the genesis, progression, proliferation, and metastasis of cancer, spices could be used to stop, prevent and/or treat cancer ^[9].



Gopalakrishnan Thamizharasi et al has reported Carvone and its derivatives have reported earlier for their anticancer effects in MCF-7 and HT-29 cell lines. Carvone has been declared to inhibit p38 MAPK signaling and invasion and induces apoptosis in myeloma cells. Additionally, D-carvone has also been reported to manifest anticancer effects in 1,2-dimethylhydrazine induced rat colon carcinogenesis by obstructing pre-neoplastic lesions, oxidative stress and abnormal activation of bio transforming enzymes. In this current study, it has been found that D-carvone at 20 and 30 mg/kg b/w doses shows chemo preventive effect against DMBA-induced skin carcinogenesis. The activities of phase I enzymes that were seriously altered upon DMBA induction were turned back to normal levels by administration of D-carvone at 20 and 30 mg/kg b.w. to DMBA induced animals, implicating the action of D-carvone against metabolic activation of DMBA. furthermore, glutathione-S-transferase (GST) detoxifies carcinogens, by wrecking their reactive centers or by easing their excretion by conjugation process ^[10].

Ila Das et al demonstrated the chemo preventive character of fresh saffron infusion on DMBA/croton oil induced skin carcinogenesis in mice. The two-stage skin carcinogenesis model in mice provide a good chance to study the efficacy of chemo preventive agents one at the initiation and other at promotional stages of carcinogenesis. Topical applications of DMBA/croton oil induce inflammation and oxidative stress-related DNA damage in skin that might cause skin papilloma. DMBA makes an adduct with genomic DNA and promotes ROS and p53 mutations that might play an important character in the promotion and progression of skin carcinogenesis, causing cell proliferation and angiogenesis. This was clearly seen from the histology of the skin samples taken from the carcinogen control mice. All saffron-treated mice exhibited marked advancement in the skin texture. Histology of the Group B mouse skin exhibits a near normal appearance when compared to normal control mice. DMBA treatments creates LPO and ROS in the affected area of the skin and finally lead to carcinogenesis. The advantageous action of saffron is certainly due to its capability to stimulate the anti-oxidant enzymes in the cells. These rises in enzyme activity effectively down-regulate the release of ROS and LPO in the skin and thus might decrease the incidences of skin papillomata on the treated areas. So, both histology and enzyme activities consider that environmental effects that lead to skin carcinogenesis can be forbidden by oral infusion of saffron in the day to day diet to reach some protection against skin cancer. The results from the current study point out that saffron can inhibit cell proliferation in addition to hyperplasia, dysplasia and papilloma growth. It was also noticed that the emergence of micro vessels was inhibited in papillomatosis and SCC by saffron ingestion, suggesting that saffron can prevent or delay angiogenesis and progression of tumors. Additional investigation is required to understand the mechanism of action of saffron compounds at the molecular level to set up saffron as an effective chemo preventive agent in cancer ^[11].

Jyoti Parmar *et al* has reported that the fruits of *Syzygies cumini* (L.) steels are eatable and reported to contain gallic acid, tannins, anthocyanins and other components. Extract of seed, which is traditionally used in diabetes, has a hypoglycemic action and antioxidant property in alloxan diabetic rats. Flavonoid diglycosidic, hydrolysable tannins (1-0- galloyl cataloging and casuarinin and a triterpene, oleanolic acid were separated from seeds of *Eugenia jambolana*. In the current study, all these constituents of *Syzygium cumini* might be in charge to reduce DMBA induced skin papilloma formation both in terms of incidence of tumor and also mean number of papilloma/ animals. It was found that quercetin significantly inhibited the expression of specific oncogenes and genes, supervising G (1), S, G (2), and M phases of the cell cycle. Furthermore, it has been shown to reciprocally up-regulate the expression of several tumor suppressor genes. Activation of these tumor suppressor genes, inhibition of expression of oncogenes and modulation of topoisomerase II activity inhibits the cell cycle thereby decrease the risk of cancer incidence, tumor burden, tumor yield and cumulative number of papillomata. Therefore, result from this study shows the anti-tumor and chemo preventive property of hydroalcoholic extract of *Syzygium cumini* seed due to the occurrence of flavonoids, quercetin tannins etc. They are employed as blocking as well as suppressing agent. Mainly flavonoids block the initiation event and therefore Group IV shows the greater decrease in tumor burden, tumor yield, tumor incidence and cumulative number of papillomata as compared to Group V. Because of the presence of quercetin in SCE, cell cycle apprehends at the point where damage occurs thereby inhibits initiation events. The results acquired from the current study clearly show that extract derived from *Syzygium cumini* seed may be effective for chemoprevention owing to have high content of flavonoids and other anti-oxidants ^[12].

Conclusions

From this current review, it has illustrated that naturally derived compounds might possibly become contributors in future skin cancer treatments. This article has outlined some of the compounds and plants that have been studied to date for their practicable anti-cancer properties. Many more unexplored resources, however, remain in mother nature. Considering this some natural products have shown the capacity for use in the symptomatic treatment of cancer, or to heal the adverse effects associated with cancer therapies, this has led to an increase in self-medication by cancer patients, pursuing safer and more effective products ^[8]. These natural ingredients may also potentially screen and reverse the damaging effects derived from solar UV radiation and additional environmental carcinogens. Combined with the use of sunscreen, this may serve as a reasonable master plan for skin cancer prevention ^[2]. The phytochemicals isolated from medicinal plants and dietary sources have exhibited great potential on dissimilar in vitro cell lines and in vivo

experimental animal models. Many epidemiological researches have also reported reverse relationship between dietic phytochemicals (fruits, vegetables) and skin cancer^[13].

References

- 1 M R Saini, P K Goyal, Geetha Choudhary. Anti-Tumor Activity of Aloe vera Against DMBA/ Croton Oil-Induced Skin Papilloma genesis in Swiss Albino Mice. *Journal of Environmental Pathology, Toxicology, and Oncology*. 2010; 29(2): 127–135.
- 2 Chau Yee Ng, Hsi Yen, Hui-Yi Hsiao, Shih-Chi Su. Phytochemicals in Skin Cancer Prevention and Treatment: An Updated Review. *International Journal of Molecular Sciences*. 2018; 19(4):941.
- 3 Simran Preet, Sanjay Bharati, Anshul Panjeta, Rupinder Tewari, Praveen Rishi. Effect of nisin and doxorubicin on DMBA-induced skin carcinogenesis a possible adjunct therapy. *Tumor Biology*. 2015; 36(11): 8301-8308.
- 4 Rajesh Agarwal, Zhi Y. Wang, Hasan Mukhtar. Inhibition of Mouse Skin Tumor-Initiating Activity of DMBA by Chronic Oral Feeding of Glycyrrhizin in Drinking Water. *Nutrition and Cancer*. 1991; (15)3-4:187-193.
- 5 Ying-Hui Kong and Su-Ping Xu. Salidroside prevents skin carcinogenesis induced by DMBA/TPA in a mouse model through suppression of inflammation and promotion of apoptosis. *Oncology Reports*. 2018; 39: 2513-2526.
- 6 Masamitsu Ichihashi, Nazim U. Ahmed, Arief Budiyanto, A Wu, Tosh nori Bitto, Masato Ueda, Toshihiko Osawa. Preventive effect of antioxidant on ultraviolet-induced skin cancer in mice. *Journal of Dermatological Science*. 2000; 23: S45-S50.
- 7 Soumya S. Bhattacharyya, Saili Paul, Sushil K. Mandal, Antara Banerjee, Naoual Boujedaini, Anisur R, Khuda-Bukhsh. A synthetic coumarin (4-Methyl-7 hydroxy coumarin) has anti-cancer potentials against DMBA-induced skin cancer in mice. *European Journal of Pharmacology*. 2009; 614(1-3): 128–136.
- 8 Tawona N. Chinembiri, Lissinda H. du Plessis, Minja Gerber, Josias H. Hamman, Jeanetta du Plessis. Review of Natural Compounds for Potential Skin Cancer Treatment. *Molecules*. 2014; 19(8): 11679-11721.
- 9 Annapoorna Sreedhar, Jun Li, Yunfeng Zhao. Next-Gen Therapeutics for Skin Cancer: Nutraceuticals. *Nutrition and Cancer*. 2018;70(5): 697-709.
- 10 Gopalakrishnan Thamizharasi, Ganapathy Sindhu, Veeran Veeravarmal, Namasivayam Nalini. Preventive effect of D-carvone during DMBA induced mouse skin tumorigenesis by modulating xenobiotic metabolism and induction of apoptotic events. *Biomedicine and Pharmacotherapy*. 2019; 111: 178-187.

- 11 Ila Das, Sukta Das, Tapas Saha. Saffron suppresses oxidative stress in DMBA induced skin carcinoma: A histopathological study. *Acta Histochemica*. 2010;112(4): 317-327.
- 12 Jyoti Parmar, Priyanka Sharma, Preeti Verma, Priyanka Sharma, PK Goyal. Chemopreventive Action of *Syzygium cumini* on DMBA - induced Skin Papillomagenesis in Mice. *Asian Pacific Journal of Cancer Prevention*. 2010; 11: 261-265.
- 13 Javed Iqbal, Banzeer Ahsan Abbasi, Riaz Ahmad *et al.* Potential phytochemicals in the fight against skin cancer: Current landscape and future perspectives. *Biomedicine and Pharmacotherapy*. 2019; 109: 1381-1393.

