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Skin Cancer: Its causes, mechanism and treatment approaches

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Abstract

Skin cancer is a prevailing problem that exist in society and it affects psychologically almost every individual because of the environmental conditions. The rate of skin cancer has been increasing continuously since past few years. Recently in 2021, 1,898,160 new cases of cancer and 608,570 cancer deaths are reported in the United States. Several therapies are available for treatment of skin cancer such as Radiation therapy, Chemotherapy, Immunotherapy, and Targeted therapy etc. There are a few conventionally available drugs already in use but are found with various side effects including skin rashes, hair loss, nausea, diarrhoea, vomiting, joint pain, etc. is BRAF is confirmed as the most important gene responsible for skin cancer by various reports. The major cause of development of skin cancer is exposure to UV rays and mutations in gene. Therefore, in future there is hope, in vivo and in vitro evaluation of plant derived phytochemicals (inhibitors) which can establish them to be the most potent V600E-BRAF inhibitors to treat skin cancer. The present review is focused on the causes of skin cancer, mechanism of spread, responsible genes, conventional treatment approaches, its side effects and benefit of phytometabolites over the existing drugs.

Review Article

Keywords: BRAF, V600E, Novel therapy, Melanoma**,** Natural Compounds

1. INTRODUCTION

Cancer is a multi- factorial disorder [1], which is caused when abnormal cells grow more aggressively that can pass through the blood stream and lymph nodes and can affect any part of body, it is also called malignant tumours and neoplasms [2]. According to WHO report 2021, abnormal cells of cancers develop very rapidly and grows beyond their usual boundaries, and spread to other organs; which is called as metastasis. Every year, the American Cancer Society declares a report that shows statistics of cancer cases and deaths that occur in a year in comparison with the most recent data. In 2021, 1,898,160 new cases of cancer and 608,570 cancer deaths are reported in the United States. The cases of melanoma are rising in US from the past few years, it estimates about 1 lakh new case will be diagnosed in 2021 and about more than 6,000 of patients have chance to die [3-4]. In a report by National Cancer Registry Program (NCRP), India indicates that, in year 2016, the estimated cancer burden was 1277 DALYs (Disability Adjusted Life Years) for a population of one lakh which is predicted to tend to increase to 26.7 and 29.8 million by the year 2021 and 2025, respectively. According to the report of American Cancer Society of 2022, about 99,780 new melanomas will be diagnosed (about 57,180 in men and 42,600 in women) and 7,650 people are expected to die of melanoma (about 5,080 men and 2,570 women). Skin cancers are the type of carcinomas that usually occur in white people, about more than 40% of cases are measured globally [5-6].

1.1 Types of Skin cancer

There are two major types of skin cancer: Melanoma and Non-melanoma. Basal cell carcinoma (BCC), squamous cell carcinoma (SCC) are categorised as non-melanoma skin cancer (NMSC) [7-8] (Figure 1, 2a). Basal cells are ball shaped located in the lower epidermis. It grows slowly which arise from inter follicular epidermal stem cells and spreads rarely over the parts of body [9]. Basal cell carcinoma (BCC) develops when the skin exposed in sun rays and 80% effect on the head and neck [10]. The damage caused by UV radiation to DNA of skin is a basic carcinogen in BCC evolution [11]. Other reasons of BCC development are the effect of sun rays and undergoing radiation therapy in some patients. Squamous cell carcinoma (SCC) develops in a flat, scale-like cell found on epidermis of skin [12]. This is commonly developed on the lips; and the skin outside the mouth, anus, and a woman's vagina. It can also develop on burned skin, the skin injured by chemicals, or unprotected skin from x-rays and almost 2% - 5% of SCC spread to other parts of the body [2].

Melanoma develop from excess growth of melanocytes cell which makes a brown colour pigment melanin in the skin [13]. Melanin protects the skin from harmful effects of sun. Mostly white skinned peoples are expected to develop melanoma in their lifetime. The highest rates of melanoma in the world mostly occur in Australia and New Zealand. The rate of melanoma diagnosis is increasing faster than any other cancer type and is now the fifth most common cancer diagnosed with an estimated one hundred thousand new cases in 2020 in the USA alone, with most occurring in white men aged 55-74.

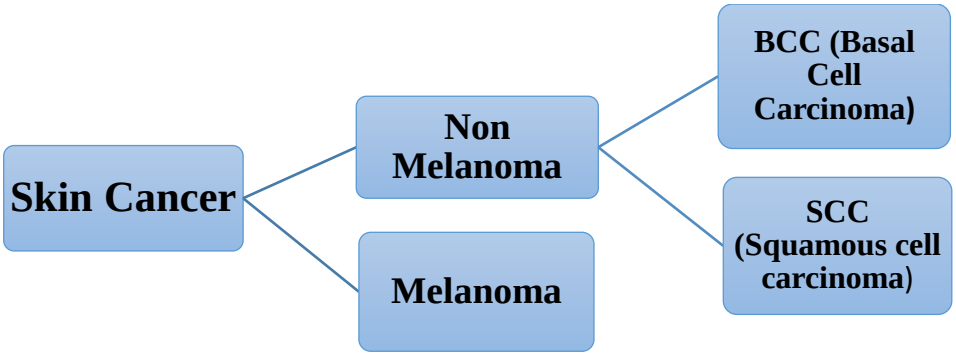

Fig 1. Types of skin cancer

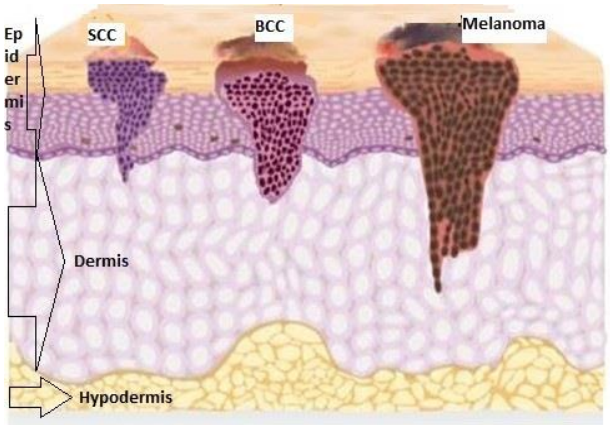

Fig 2 a). Skin cancer permeation through the epidermal layer of skin [14]

1.2 Mechanism of melanoma development

Cancer grows when one or more genes in a cell are mutated (changed), creating an abnormal protein. The most common activating mutation in BRAF is a substitution of valine for glutamic acid at amino acid 600 (V600E) [30], which was employed as a driver mutation in these mouse models (Figure 2 b).

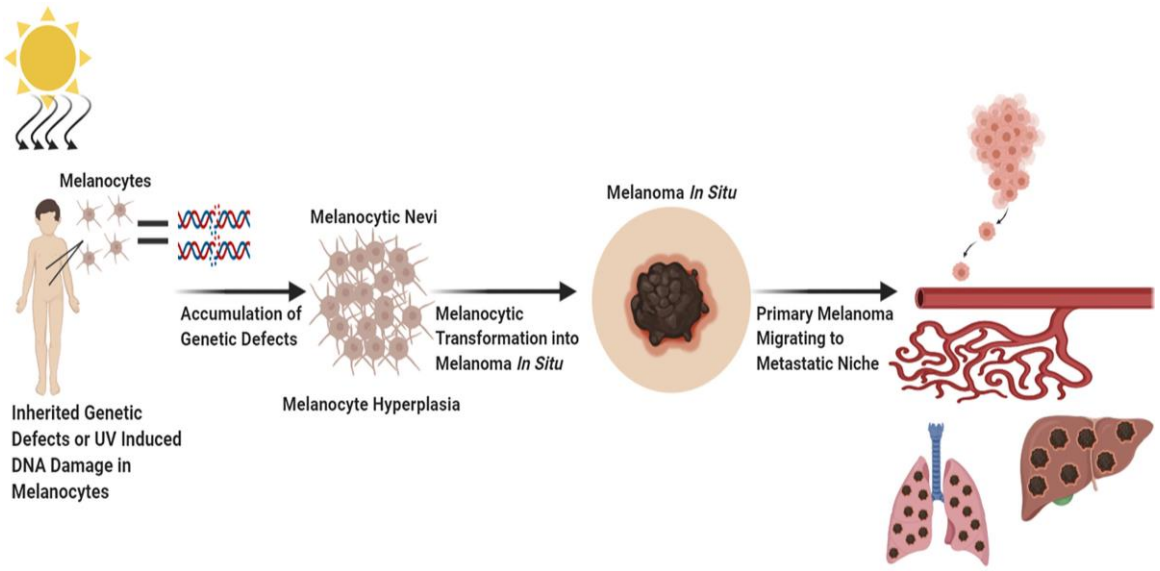

Fig 2 b) Development of melanocytic transformation [31].

2. Risk factors of developing skin cancer

Appearance of skin cancer depends on both environmental and constitutional factors [15]. Exposure to UV-rays is the major environmental risk factor for BCC, SCC and melanoma (AAD, 2016), and skin phenotypic characteristics are one of the major constitutional risk factors. The Centre for Disease Control and Prevention (CDC) provides the statistics that enlists various causes of skin carcinoma. The CDC explained the way of indoor tanning exposed individuals to UVA and UVB rays or both can lead to skin cancer. Those who began tanning during adolescence have exhibited higher risk of developing melanoma in adulthood. About 90% of chances of skin cancer are caused due to excessive exposure in UV rays [16]. The risk of skin cancers is rising due to mutated gene of melanoma and non-melanoma passes down to one generation to another in a family. According to American Cancer Society, causes of cancer are not completely understood, but some factors can increase the risk like e.g. tobacco use and excess body weight etc. According to the report of world cancer research fund international, drinking of water contaminated with arsenic and consumption of alcoholic drinks might increase the risk of malignant melanoma and BCC (Figure 3).

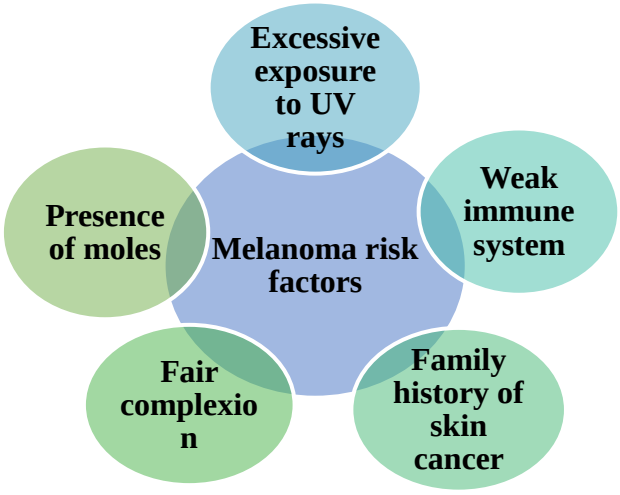

Fig 3 Risk factors of induction of melanoma

2.1 Risk reduction

Some studies have proved that drinking coffee might decrease the risk of malignant melanoma in women and BCC (Basal Cell Carcinoma) in men and women [17]. There is 59% chance of survival, if the melanoma affects 3 mm depth, if it is not entered into blood stream it can removed by simple surgery [18]. Reports confirms

that over 95% of patients can recovered from skin cancer if it is detected and treated in the early stages [19].

2.2 Existing Treatment Approaches and their Side effects

There are different medical modalities available for the treatment of skin cancer perhaps it comes with various side effects. The following are the treatments of skin cancer along with their side effects:

Radiation therapy: It uses high-energy x-rays or particles (like photons, electrons, protons) to kill cancer cells. Side effects caused by radiation therapy include skin irritation, redness, changes in skin colour, hair loss intreated area, damage to saliva-making glands and teeth [20].

Targeted therapy: Drugs directly attack melanoma cells, target a gene and inhibit the cells to grow. Side effects include fever, headache, fatigue, thickened skin.

Chemotherapy: In chemotherapy, drugs goes through body and attack the cancer cells. Some chemotherapy drug is pills. Chemo not only kills cancer cells, it also kills fast dividing cells and thus, the side effects includes hair loss, nausea, vomiting and diarrhoea.

Immunotherapy: It is also known as Immune checkpoint blockade (ICB) therapy [21]. It uses effective drugs which helps immune system to find and attack cancer cells, and simultaneously it affects the healthy cells also leading to itching, rashes on skin, constipation, joint pain as side effects.

3. Role of genes in skin carcinoma

Large number of genes were identified for their role in skin cancer including inherited and non-inherited genes. Inherited gene mutations include CDKN2A, MDm2, CDK4, RB, MC1R, TYR, TYRP1, ASIP [22] and Non-inherited gene mutation include BRAF, CDKN2A, EGF, Fas, PTEN [23]. Some genetic defects that are acquired due to environmental factors are mutations in BRAF, NF1 (Neurofibromatosis type 1), and NRAS (Neuroblastoma Rat Sarcoma Virus) that arise from exposure to UV light which damage the DNA of skin. The mutation in the BRAF gene is most commonly found in 50% of all melanomas. Some other genes are also affected such as NRAS, CDKN2A (cyclin dependent kinase inhibitor 2A), and NF1, generally only one of those genes can be affected in skin cancer [22]. The most common activating mutation in BRAF is a substitution of valine for glutamic acid at amino acid 600 (V600E) [24]. Studies have identified that non-inherited mutation in the BRAF gene that appears to be the most common event in the process leading to melanoma. Researchers have studied that mutations in non- inherited BRAF gene is the most common mutation that leads to melanoma [25].

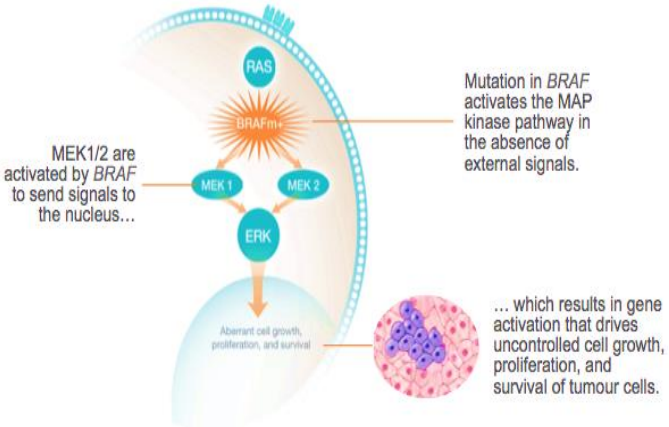

Fig 4 Oncogenic BRAF drives uncontrolled growth of tumour and proliferation [27, 28].

BRAF gene is located in long arm of chromosome 7 and codes for serine/threonine protein kinase [26]. BRAF makes a Protein called B-Raf that helps melanoma cells to grow. Activating BRAF mutation has been estimated to

occur in approximately 50% of cases of melanoma. MEK gene is also a part of BRAF gene. The mutations in melanoma drives through signal transduction pathway called mitogen activated protein kinase (MAPK) pathway for cell growth, proliferation, and survival. About half of melanomas have mutation in BRAF gene. Drugs which block the MEK protein (MEK inhibitor) can help to treat melanoma with BRAF gene changes.

New adjuvant therapies are available, including immunotherapies which target MAP kinase pathway [23], to inhibit abnormal cell growth of BRAF or MEK gene, by giving inhibitors [27].

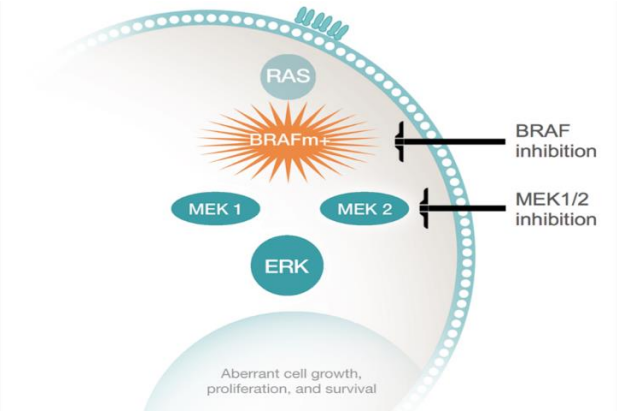

Fig 5 BRAF and MEK inhibition target the MAP kinase pathway [27, 28].

Schadendorf *et.al* in 2019 [29] described the overview of melanoma and the treatments that target BRAF with V600 mutations using selected BRAF inhibitors combined with mitogen-activated protein kinase inhibitors have significantly improved response and overall survival.

4. Natural Compounds and Secondary Metabolites

Various treatments for malignant melanoma and non- melanoma skin cancers are available, but chemotherapies have low success rates due to the development of multi-drug resistance [32]. It determines the importance of new compounds to be explored that could be safe and effective against skin cancer. Common anti-cancer effects of natural compounds are inhibition of cell proliferation and metastasis. Anti-melanoma effects of natural compounds go in the body through different pathways for the inhibition of angiogenesis and the effects of tumour promoting proteins such as PI3-K, Bcl-2, STAT3 and MMPs [33]. Natural products have made a major contribution in pharmaceutical industry for making novel drugs, especially for the treatment of cancer and infectious diseases [34]. There are only few naturally derived drugs that exist in the market which are used to target skin related cancers, whereas none have been approved yet for topical application [33]. There are some inhibitors which target protein like BRAF or MEK to treat melanomas, especially the combined drugs of BRAF or MEK can shrink many tumours that gives positive results for the BRAF gene mutation. Now a days the researchers are looking for the drugs which could be helpful before and after surgery of melanomas. There are some selected plant species having compounds of anticancer activity which could be helpful for treatment of skin cancers and could be prepared as a novel drug for target therapy of treatment. Millsop et.al. in 2013 [35] reported the natural compounds obtained from herbs, stems, roots, and other parts of plant that have been used to treat NMSC and that may suppress or reverse the process of carcinogenesis.Chinembiri*et.al* in 2014 [36], explained that anti-cancer drugs are generally obtained from natural resources like marine, microbial and botanical sources. Therefore, in future the naturally derived compounds could be able to play a key role in the treatment of

melanoma. The natural compounds are used traditionally for cancer treatment is cheap due to the easily obtaining of plants and their processing are simple to prepare a product.

CONCLUSION

This review is an attempt to show the benefits of natural metabolites to improve the treatment of skin cancer as compared to other conventional therapies because the molecules obtained from plants are attractive alternative to other treatments because several plant-derived compounds have exhibited lower toxicity and higher selectivity against cancer cells.

Conflicts of Interest: None.

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