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Review

A Comprehensive Review of Various Therapeutic Strategies for the Management of Skin Cancer

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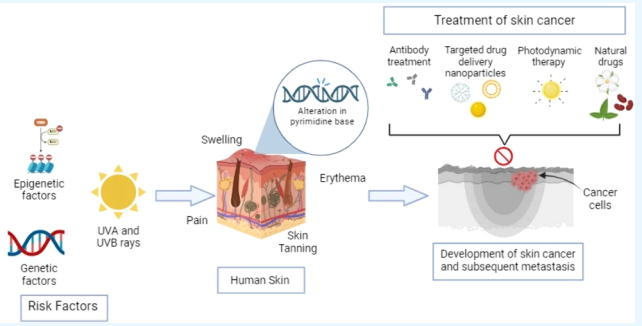
ABSTRACT: Skin cancer (SC) poses a global threat to the healthcare system and is expected to increase significantly over the next two decades if not diagnosed at an early stage. Early diagnosis is crucial for successful treatment, as the disease becomes more challenging to cure as it progresses. However, identifying new drugs, achieving clinical success, and overcoming drug resistance remain significant challenges. To overcome these obstacles and provide effective treatment, it is crucial to understand the causes of skin cancer, how cells grow and divide, factors that affect cell growth, and how drug resistance occurs. In this review, we have explained various therapeutic approaches for SC treatment via ligands, targeted photosensitizers, natural and synthetic drugs for the treatment of SC, an epigenetic approach for management of melanoma, photodynamic therapy, and targeted therapy for BRAF-mutated melanoma. This article also provides a detailed summary of the various natural drugs that are effective in managing melanoma and reducing the occurrence of skin cancer at early stages and focuses on the current status and future prospects of various therapies available for the management of skin cancer.



1. INTRODUCTION

Cancer is characterized by deregulated cell growth comprising different disease groups.[1] It originates from a combination of epigenetic and genetic abnormality that leads to the turn-off of anti-oncogenes and the switch-on of oncogenes/proto-oncogenes.[2] There were 19.3 million new cases of cancer globally in 2020 and about 10 million cancer-related deaths occur yearly.[3,4] Globally, skin cancer (SC) is the fastest-growing cancer type, which is characterized by an aggressive, persistent, multifaceted cancer.[5,6] The various kinds of skin tumors have been designated following the cells from which they develop, with squamous cell carcinoma (SCC) and cutaneous melanoma (CM) as well as basal cell carcinoma (BCC) among the most prevalent and well-characterized.[7] A majority of cutaneous tumors (around 90%) are nonmelanoma skin cancer (NMSC).[8] When therapy is insufficient or slowed down, NMSC may be locally damaging even though they are typically treatable and seldom lead to mortality or advanced stages. On the other hand, CM, which comprises nearly one percent of skin tumors that pose the greatest risk of mortality, is responsible for 90% of skin-tumor-related fatalities.[9]

Epidermal cells are the main cause of NMSC, which exhibits typical epidemiology (for example, a higher incidence in Caucasian people). On the other hand, MCC, which is hypothesized to result from Merkel cells, is more common in equatorial regions and is more common in people of white ancestry.[10] Although there are several factors involved in the pathogenesis of BCC, SCC, and MCC, exposure of the skin to environmental cancer-causing agents is the most common cause of risk. Progenitor cells may immediately undergo a cancerous change due to ultraviolet radiation (UVR).[11−13] Other risk factors for the growth of BCC and SCC involve co-occurring illnesses and therapies (such as psoriasis), repeated contact with the human papillomavirus, drug-induced suppression of immunity in patients with transplants, and specific medications for the management of various kinds of cancer (particularly melanoma).[14−16] The growth of NMSC is favorably influenced by poor socioeconomic and demographic positions, as shown by numerous research.[17,18] A frequent occurrence in MCC is the inclusion of the Merkel cell polyomavirus (MCP-yV) inside the genome of tumor cells. In recent years, the molecular characteristics underlying the MCP-yV-induced cancerous alterations in Merkel cells have

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now been clarified.[19] Even though SCC and MCC are characterized via a large neoantigen burden, dysregulation of the Wnt/Hedgehog system has been suggested as a potentially crucial factor in the formation of BCC.[19−21]

The most lethal skin tumor, however, is CM, which makes up just 1% of skin cancers yet is responsible for 90% of fatalities brought on by skin cancer. Over 320,000 fresh diagnoses of CM were reported globally in 2020, leading to 57,000 deaths and over 1.2 million new cases of NMSC, based on the most current GLOBOCAN projections.[13] Due to difficulties with NMSC identification and documentation, the final figure could be significantly underestimated.[22] The elevated skin tumor rate of death is primarily due to delayed diagnosis, which is triggered by nonspecific symptoms,[23] lack of reliable screening techniques,[24] a lack of precise and sensitive biomarkers for prompt detection, prognosis, and therapy monitoring,[25] and a lack of knowledge of the mechanisms underlying resistance to drugs in these tumors.[26] Therefore, over the past two years, the COVID-19 pandemic, which has taken a lead role in everyday clinical practice, has limited the availability of medical services and delayed the detection of individuals with CM and other skin tumors, leading to higher rates of illness and death, and as a consequence, more financial strain on medical facilities.[27] There is a need to identify safer biomarkers to speed up identification, prognosis, and response to therapy among individuals with advanced-stage skin malignancies given their poor prediction.[28]

2. SKIN CANCER OCCURS DUE TO THE INVOLVEMENT OF VARIOUS FACTORS

The DNA of skin cells is damaged due to overexposure to UV radiation and chemical alteration to certain pyrimidine dimers, which occurs because UV rays are absorbed by the nucleotides.[29] SC is mostly caused by an amalgamation of both modifiable (such as environmental) and nonmodifiable (such as genetic) factors. The most frequent SC risk factor is modifiable.[30]

2.1. Modifiable Risk Factors. UV exposure has the greatest impact on the risk of SC. Production of melanin is stimulated due to UV exposure to melanocytes, and the skin appears tanned indicating impairment to the skin, DNA, and skin cells; if strong, exposure leads to a sun tan, which signifies cell mortality.[31]

2.2. Categories of UV Radiation. UV radiation has three subcategories UVA, UVB, and UVC.[30] The ozone layer does not absorb UVA, thus they deeply penetrate the skin via an epidermal junction. The shorter wavelength is UVB rays. UVA and UVB produce skin tans.[32,33] Swelling, erythema, and pain are caused due to overexposure to UVB radiation. The shortest rays are UVC radiation, and the ozone layer absorbs these rays.[34]

2.3. Role of UV Exposure. The progression of various types of melanoma is linked with UV radiation exposure patterns.[35] Long-term susceptibility such as occupational outdoor exposure is frequently linked to SCC and BCC SC.[36,37] The superficial BCC usually appears on the trunk.[38] As compared to SCC, melanoma is commonly associated with irregular exposure.[39] Traditionally outdoor workers are believed to have a higher risk of developing SCC and BCC.[40] Combining 15 studies, a mutual analysis displayed increased melanoma risk for outdoor workers working in areas where exposure to UV is higher.[30]

2.4. Occupational UV Exposure. The risk of melanoma increases due to occupational exposure to UV rays among outdoor workers. It has been demonstrated by various studies that outdoor workers are at augmented risk of SCC and BCC.[41] Research does not find an augmented risk of SC among outside workers.[42] Still, studies examining UV-intense areas for outdoor workers have displayed that workers have a high chance of having SC on the neck and head.[43]

3. ROLE OF GENETIC FACTORS IN SKIN CANCER

Genetic factors (family history) trigger melanoma risk. The person's features induce the risk of melanoma like blonde or red hair, light-colored eyes, naturally fair skin tone, nevi or moles, and dermal areas that burn, freckle, and redden.[44] Skin diseases such as melanoma and nonmelanoma SC are caused by a variety of skin diseases, including altered protein synthesis caused by genetic factors that contribute to the development of SC.[45,46] Immunosuppressed patients are more likely to develop cutaneous malignancies than healthy people. An integrated multidisciplinary approach involving dermatologic surgery, radiation oncology, and medical oncology is necessary for the management of such patients.[47] There are connections between certain viral infectious diseases, such as AIDS, and SC. It has been noted that AIDS patients have a 3- to 5-fold higher risk of having nonmelanoma SC.[48] Furthermore, it is found that the incidence of BCC is 11.4-fold higher in HIV-positive hemophiliac patients than in the general population. HIV patients with SCC have a 50% mortality rate between the ages of 6−84 months and a high risk of metastasis.[49] About 90% of NMSC in immunosuppressed patients and up to 50% in immunocompetent patients were found to contain DNA originating from cutaneous or b-HPV types, according to molecular studies that reveal the complicity.[50] It is also believed that these viruses may contribute to the pathogenesis of nonmelanoma SC indirectly.[51] It has been discovered that patients with xeroderma pigmentosa are more likely to experience sunburn, freckling, and childhood skin.[52] SC, including melanoma and nonmelanoma SC, frequently have dysregulated signaling pathways linked to the regulation of gene expression. One such dysregulation is the PTCH1 gene mutation, which causes uncontrollable skin cell proliferation and multiplies BCCs.[53] Similarly, in men, a CDKN2A gene mutation is the most frequently found cause, whereas, in women, MDM2 gene mutations are predisposed to melanoma development at an earlier age.[54]

4. ROLE OF EPIGENETICS IN SKIN CANCER

In the year 1942, biologist Conrad H. Waddington first described the term "epigenetics" as the "study of the heritable alteration in the expression of the gene, mediated via mechanisms excluding variations in the primary nucleotide sequence of a gene".[55,56] Histone modifications, chromatin remodeling, and noncoding RNA (ncRNA) mediation are the main forms of epigenetic modification.[1,57] Groups of DNA methyltransferases (DNMTs) execute demethylation reactions and DNA methylation.[58] Transfer of the methyl group from *S*-adenosyl methionine (SAM), a one-carbon metabolite, to the fifth position of cytosine catalyzed these enzymes, which form into 5-methylcytosine (5mC).[59] From various DNMTs, during the replication phase, DNMT1 performs the methylation reactions, although DNMT-3a/b carries out the de novo reaction. Furthermore, methylation of DNA is distributed

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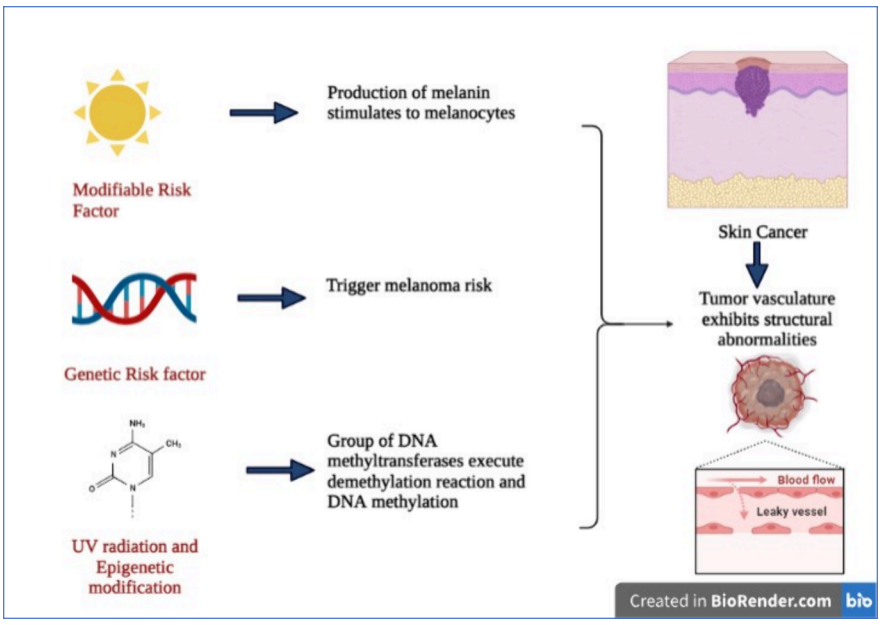

Figure 1. Formation of the tumor and its entry through the leaky vasculature of cells and major causes of skin cancer (created with BioRender.com).

mainly at 10% in CpG islands (CGIs) and CpG-dense regions at 60−80%.[60] One study found that CGIs primarily reside in the transcriptionally active regions and are unaffected by methylation through a variety of mechanisms like occupied TFs, RNA pol II, or H3K4me3, and nucleosome positioning is driven by DNMT blockage.[61] It becomes transcriptionally silenced if CGI becomes condensed in the promoter region. In contrast, via a sequence of enzymes, i.e., 10−11 translocases (TETs) known as TET1/2/3-governed-reactions, DNA that has been methylated can be changed back to its original cytosine base.[1] The 5mC (5-methylcytosine) can be oxidized by TETs to yield 5fC (5-formylcytosine), 5hmC (5-hydroxymethylcytosine), and 5caC (5-carboxylcytosine).[62] Base excision repair transformed 5caC and 5fC to a cytosine base by coupling with thymine DNA. However, from any of the above intermediates, the mechanism can also be changed by a replication-governed mechanism to cytosine synthesis.[63] Moreover, by recruiting suppressing transcription factors or binding or recruiting proteins, DNA methylation can repress gene expression, consequently revealing rare proof of DNA-methylation-governed transcriptional activation,[1,64] shown in Figure 1.

5. RISK FACTORS AND METASTASIS RISK OF SKIN CANCER

5.1. Immunosuppression. For patients with immunosuppressed states having rapid growth of cutaneous squamous cell carcinoma, it generally recurs locally in the second year after excision in 13% of patients, and patients have a 5−8% risk of metastasis. For older patients with tumors on the skin of their head and neck, the prognosis is typically worse if there are multiple tumors present and if the patient has a history of excessive sun exposure.[65] Immunosuppression in patients is mainly diagnosed by blood tests.[66]

5.2. Testicular Germ-Cell Tumors (TGCT). Among young adult men, testicular germ-cell tumors (TGCT) are the most prevalent cancer. Previous research suggested that TGCT survivors are more likely to develop SC. Among TGCT survivors, the standardized incidence rates for SC and melanoma were 1.93 (95% CI, 1.62−2.29, P = 0.0001) and 1.81 (95% CI, 1.57−2.08, P = 0.0001), respectively.[67]

5.3. Administration of Anti-Epileptic Agents/Drugs (AEDs). The majority of anti-epileptic medications were not linked to SC. SCC was linked to the use of carbamazepine (OR, 1.88; 95% CI, 1.42−2.49) and lamotrigine (OR, 1.57; CI, 1.12−2.22), with carbamazepine showing evidence of a dose−response relationship. The estimated absolute risks were low; for instance, one additional SCC required 6335 person-years of high cumulative exposure to carbamazepine.[68] Compared to other AEDs, lamotrigine and carbamazepine most likely increase the skin's sensitivity to sunlight. According to reports, these two AEDs have the ability to photosensitize due to their photochemical characteristics and ability to cause photosensitivity reactions. AEDs and other photosensitizing medications may raise the risk of skin cancer by making people more sensitive to UV radiation.[68,69]

5.4. Human Papillomavirus (HPV) Infection and Human Immunodeficiency Virus (HIV) Infection. After adjusting for sex, age, and comorbidities, the adjusted hazard ratio of SC for patients with HPV in comparison to controls was 2.45 (95% CI, 1.44−4.18, P < 0.01). A patient with HPV infection had a significantly higher risk of SC if they were older than 40 years, according to the subgroup analysis.[70] Patients with HIV are more likely to develop BCC and SCC. When compared to HIV-uninfected individuals, SCC had the highest correlation and statistical significance, with a prevalence ratio of 5.1. HIV-positive people were 80% more likely to develop skin cancer than HIV-negative people (95% CI, 1.3−2.4, P = 0.001). Patients' ages were associated with a 45-fold increase in risk (95% CI, 3.3−15.9, P = 0.001). After adjusting for patient age, sex, and race, the likelihood of developing cancer was 6.4 times higher than that of the other (95% CI, 49−84, P = 0.001). HIV infection increases the likelihood of acquiring HPV, which includes oncogenic viruses, because of immunosuppression treatment and high-risk behavior.[71]

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Table 1. Risk Factors of Skin Cancers, Identification Test, and Skin Metastasis Risk

risk factors	identification	skin metastasis risk	references
immunosuppression	blood tests	recur locally in 13% of patients and have a 5−8% risk of metastasis	65
ultraviolet (UV) radiation	histopathology	DNA base pairing mainly UV−B and UV−C, damage double bonds of pyrimidines	77
testicular germ-cell tumors (TGCT)	biopsy	SC and incidence melanoma among TGCT patients were 1.93 (95% CI, 1.62−2.29, $P < 0.0001$) and 1.81 (95% CI, 1.57−2.08, $P < 0.0001$)	67
administration of anti-epileptic agent/drugs (AEDs)	histopathology	use of some AEDs involving phenobarbital (OR 0.49, 95% CI, 0.25−0.95), pregabalin (OR 0.61, 95% CI, 0.34−1.09), clonazepam (OR 0.71, 95% CI, 0.42−1.20) and valproic acid (OR 0.75, 95% CI, 0.51−1.09)	68
human papillomavirus (HPV) infection	histopathology	the adjusted hazard ratio (HR) of SC for patients with HPV relative to controls was 2.45 after adjusting for sex, age, and comorbidities (95% CI, 1.44−4.18, $P < 0.01$)	70
smoking	histopathology	smoking is related to a high risk of SCC (pooled R, $R = 1.32$, 95% CI, 1.15, 1.52), but the risk with BCC and MM is very low (pooled R, $R = 0.85$, 95% CI, 0.75, 0.96 and pooled R, $R = 0.72$, 95% CI, 0.64, 0.82, respectively)	72
Li−Fraumeni syndrome	genetic biomarker	the risk of SC at the age of 40 is 10.4% (95% CI, 4.4−23.5%), at age 60 it is 25.2% (95% CI, 12.3−47.6%), and at age 70 this risk is 44.6% (95% CI, 22.9−73.9%)	76

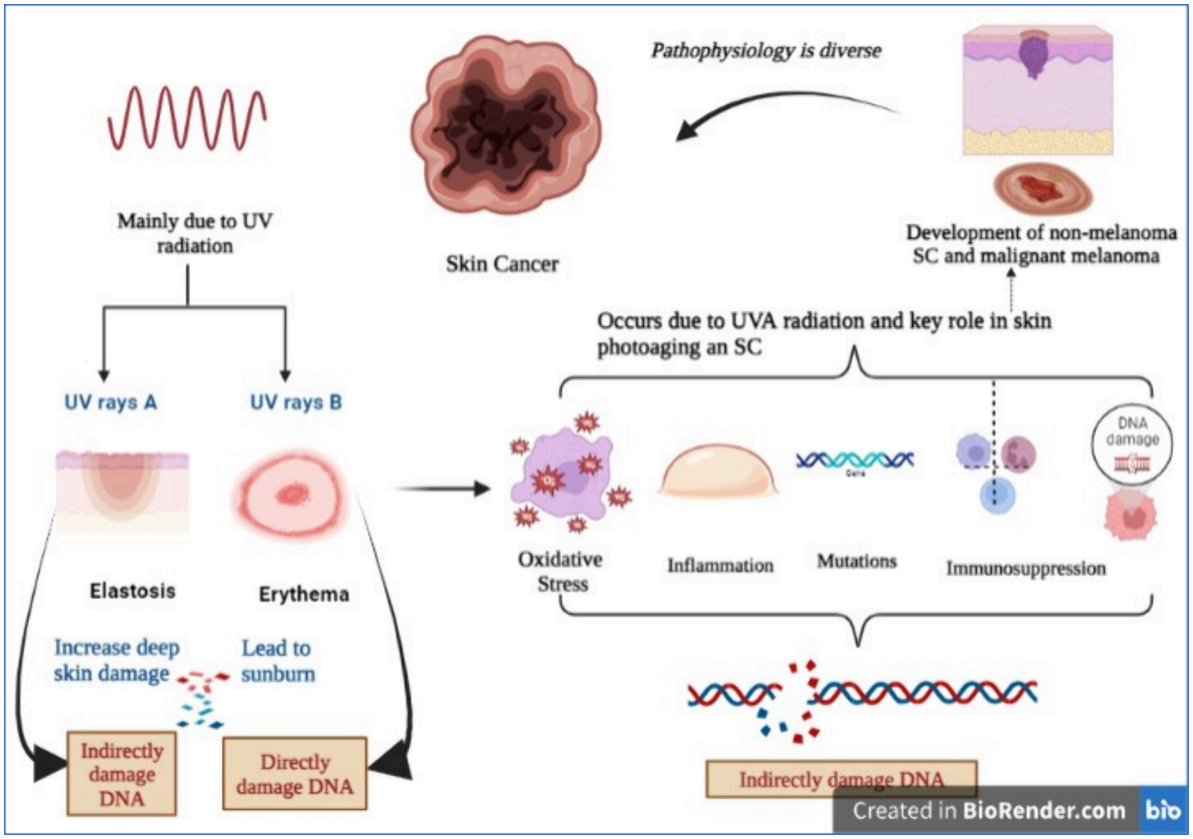

Figure 2. An illustrative image describes the pathogenesis of skin cancer, which is mainly observed due to UV rays (UVA and UVB); direct or indirect damage to DNA then produces oxidative stress, inflammation, mutation, and immunosuppression (created with BioRender.com).

5.5. Smoking. Current smoking increased the risk of SCC (pooled RR = 1.32; 95% CI, 1.15, 1.52) but decreased the risk of BCC (pooled RR = 0.85; 95% CI, 0.75, 0.96) and MM (pooled RR = 0.72; 95% CI, 0.64, 0.82). There was no evidence of publication bias, and no one study significantly influenced the combined findings. While former smoking was not linked to an increased risk of SC, similar results were found for heavy smoking.[72] The induction of specific mutations in the p53 gene could exert its carcinogen effect on human skin.[72,73] A second possible effect of smoking in the development of cutaneous SCC could be the loss of immune surveillance since smoking has been shown to suppress immunologic functions,[74] and immunosuppressed patients are known to have an increased risk of SCC.[75]

5.6. Li−Fraumeni Syndrome. An inherited cancer syndrome called Li−Fraumeni syndrome (LFS) is marked by the early onset of several different cancers. A germline TP53 gene mutation is connected to LFS. There were 71 patients (59% of whom were female) and 33 families in total. A median age of 41 (25−65) years was reached by 10 patients (14%) who had a total of 19 SC. A person's lifetime risk of developing SC is 10.4% (95% CI, 4.4−23.5%) at age 40, 25.2% (95% CI, 12.3−47.6%) at age 60, and 44.6% (95% CI, 22.9−73.9%) at age 70,[76] summarized in Table 1.

6. PATHOGENESIS OF SKIN CANCER

SC pathophysiology is diverse. The development of non-melanoma SC and malignant melanoma is due to UV

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radiation.[78] UV radiation is further subdivided as mentioned below.[79]

I. UVA (Ultraviolet A)
II. UVB (Ultraviolet B)

UVA radiation increases deep skin damage (elastosis) by passing deeper into the skin than UVB rays.[80] UVB radiation leads to sunburn or erythema. DNA damage, immunosuppression, gene mutations, inflammatory responses, and oxidative stress occur due to UVA radiation, and all of these play a key role in skin photoaging and SC.[81] The DNA is directly damaged by UVB radiation while UVA indirectly damages the DNA, which occurs by damage to cellular membranes and free radicals.[82] An interrelation between UV-radiation-induced immunosuppression and SC genesis is demonstrated by researchers. UV radiation is carcinogenic because it promotes tumor formation by promoting mutations in anti-oncogenes and also initiates tumor development.[83] UVA radiation plays a significant role in the carcinogenesis of stem cells of the skin and by inflammatory responses and tumorigenesis, and UVB promotes DNA damage.[84] In the skin when UV radiation penetrates the DNA of the epidermal layer, keratinocytes absorb much of its energy. According to the assumption of researchers, the photoreceptor in the skin is DNA, and UV rays triggering the formation of a cyclobutane pyrimidine dimer is the early molecular step that decreases immunity.[85] The mechanism of having SC by UV-radiation-induced damage is complex and intricate. UV radiation leads to mutations to p53 (anti-oncogene genes) that repair DNA or promote cell death of cells whose DNA is damaged. So, they are not involved in the DNA repair process if p53 genes are altered/mutated.[86] This deregulation of apoptosis promotes unchecked keratinocyte mitosis, and the development of SC begins. UV-radiation-induced free radical damage is a prime mechanism of carcinogenesis, and patients are predisposed to skin tumors due to their genetically determined ability to metabolize free radicals.[87] The role of antioxidants played by the enzyme glutathione *S*-transferase (GST) is to decrease the toxic effects of ROS.[88] The enzyme glutathione *S*-transferase polymorphisms (GSTP) is expressed broadly in the epidermis and dermis of the skin, and the development of SC is a vital mediator. The GSTP gene deletion increased susceptibility to the developed SC.[89] Alterations in color, size, shape, mole surfaces, and other skin lesions or new growth on the skin are important signs of cutaneous carcinoma development.[90] Generally, the alterations that are found over a few days are not tumors, but alterations that last for a month or more should be evaluated by a physician,[91] as shown in Figure 2.

7. THERAPEUTIC STRATEGIES FOR THE TREATMENT OF SKIN CANCER

7.1. Ligands. Targeting antitumor medications to solid tumors at the specific therapeutic concentration is still challenging.[92] To address this issue, a promising approach is to use ligands that specifically target and enter tumor cells and/or cells within the tumor microenvironment while avoiding noncancerous cells. Various ligands can be utilized for targeting like antibodies, nanobodies, peptides, proteins, etc.[93]

7.2. Approaches to Detect New Ligands. The discovery of targeting approaches that have minimum interaction with the healthy tissue is still needed for finding novel targeting molecules that have high specificity for cancers.[94] It is highly desirable to develop new ligands with multiple targeting capabilities to combat the difficulty and aggressivity of the tumor microenvironment.[93] "Phage display technology" is a technique for recognizing new peptides and antibodies that target a specific receptor. It was developed in the year 1985.[95]

7.3. Therapeutic Approaches for SC Treatment via a Ligand. The radio-sensitizing and photosensitizing properties of gold nanoparticles conjugated to 5-aminolevulinic acid (5ALA) were demonstrated.[96] CLEC2A is the ligand of the NKp65-triggering NK cell receptor. It was found in sporadic dermal cancer-linked fibroblasts. Dermal fibroblasts that express CLEC2A are crucial for the immune control of the skin.[97] A new ruthenium-consisting PS was developed by groups of researchers that modulate biological and photophysical properties to better meet PDT requirements.[98] Interestingly, it was discovered that cells in the mitotic phase were more impacted and had a unique apoptosis mechanism.[99] In ALA-based PDT, ALA esters or 5-aminolevulinic acid (ALA) are utilized as pro-drugs to promote the synthesis of the powerful PS protoporphyrin IX (PpIX).[100] The production of ROS and toxic responses is caused by the activation of PpIX by light. Studies have shown that butyric acid (GABA) transporters are included in ALA uptake and its methyl ester (MAL) into cells.[101] Therefore, the creation of inhibitors that specifically target particular GAT subtypes and the homology models may be a benefit in the design of therapeutic inhibitors that can be used to reduce the pain caused by ALA.[102] Branched polyethylenimine (BPEI)-modified Eu^{3+} and YVO4:Bi^{3+} NCs (nanocrystals) were prepared, an epidermal growth factor (EGF) and folic acid (FA) were bound to the BPEI-coated Eu^{3+}, and the YVO_4:Bi^{3+} NCs showed low cytotoxicity and efficient targeting of fluorescent NCs to the targeted overexpressed folate receptor in HeLa cells or EGFR in A431 cells.[103] 5-Fluorouracil (5-FU) combined with calcipotriol increases HLA class II, thymic stromal lymphopoietin (TSLP), and the natural killer cell group 2D (NKG2D), and there are benefits of combining calcipotriol with 5-FU therapy in maximizing $CD4^+$ T-cell-mediated immunity activation against SC and other cancers.[104]

7.4. Targeted Photosensitizers. *7.4.1. Folate (FA) and Transferrin (TF).* The most used targeting ligands are FA and TF, included in photodynamic therapy (PDT). While the targeted delivery of photosensitizers (PSs) is more often investigated in nanocarriers, the production of bioconjugates with enhanced selectivity for cancer cells is described by investigators.[105] Although improved internalization by cancer cells is lacking studies, this work for the manufacture of new FA-targeted PS conjugates can serve as a guideline.[106] Platinum porphyrin and FA form a complex from carboxylic acid activation, permitting its amide bond formation with the linker and yielding a novel FA-targeted PS selective for FRα-positive cell lines. Confocal microscopy studies confirm the endocytosis of targeted PS by HeLa cells, which contrasts with the FRα-negative cell line.[93,107] Phototoxicity assays show the PS's selectivity, with a 78% reduction in viability of the FR-positive cell line compared to the FR-negative line, a difference of 25%.[93] Furthermore, transferrin, FA, and different endogenous ligands have been researched for anti-tumor-targeted PDT.[108] FRα is less overexpressed than biotin receptors in various cancer cell lines of distinct histological origins.[109] It is signified by elevated selectivity and increased aggregation in tumor cells via Biotin-targeted PS.[110]

7.4.2. Nanobody and Antibody. Antibodies targeting PSs and other fractions create a division of molecules that are

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utilized for the delivery of PSs, and with the advancement of customized medicine, it has gained popularity.[111] The probable synthetic approaches for the advancement of tetrapyrrole-based antibody−PS conjugates are cysteine (maleimide conjugation) or conjugation through lysine (isothiocyanate and amide conjugation), alkyne−azide cycloaddition promoted by strain but without copper, and SNAP−Tag conjugation and chemistry (copper-catalyzed alkyne−azide cycloaddition).[93,112]

7.4.3. Peptide-Targeted PS. The targeted delivery of PS promotes aqueous solubility with the aid of small peptides that increase therapeutic efficacy and phototoxicity.[113] Solid- or solution-phase approaches provoke activations of carboxylic acid. Phage display against EGFR identified the peptide GE11 that attracted the attention of various researchers.[114]

7.5. Natural Compounds Used in the Management of Skin Cancer. *7.5.1. Saffron.* Saffron (*Crocus sativus* L.) is a traditional medicine that belongs to the family Iridaceae.[115] Crocin is an active constituent of saffron that is widely used to treat various types of cancers; on the other hand, it arrests the cell cycle in leukemia cells.[116] Moreover, its apoptotic property and the mechanism of crocin was studied on skin cancer cells (A431 and SCL-1). It decreases the expression of STAT/JAK circuits while restricting the cell cycle in G0/G1 and inhibiting cell propagation of human skin cancer cells.[117]

7.5.2. Green Tea Polyphenols (GTPs). GTPs are obtained from *Camellia sinensis* (family Theaceae) and contain anticancer (prostate cancer), antimicrobial, antidiabetic, anti-atherosclerotic, and anti-obesity activity.[118−120] The researcher found that regular administration of green tea polyphenols reduces the occurrence of nonmelanoma SC via triggering DNA repair, preventing inflammation, and inhibiting IL-1β production, leading to suppression of melanoma skin cancer growth. Furthermore, it is also found that GTPs induce miR-29 attenuation and block tumor growth by suppressing DNA hypermethylation.[121]

7.5.3. Diosmetin. Diosmetin is a naturally occurring flavonoid mainly derived from citrus fruits.[122] Over the past three decades, diosmetin has been shown to have a variety of therapeutic effects like anticancer activity on breast cancer as well as antioxidant, antibacterial, and anti-inflammatory activity.[123,124] The previous study demonstrated that diosmetin prevents the development of a tumor and suppresses angiogenesis in SC. The results of this study revealed that diosmetin blocks the migration of SC cells and also induces apoptosis via regulating caspase circuits.[125]

7.5.4. Cantharidin (CTD). Cantharidin is a poisonous monoterpene obtained from blister beetles that belong to the order Coleoptera and family Meloidae.[126] It can be used to treat various types of cancer like hepatic cancer, leukemia, breast cancer, and other diseases.[127] It was found that it suppresses the MAPK (p38, JNK, and ERK) signaling pathway via decreasing NF-κB and AKT, resulting in down-regulation of MMP-2/-9 and uPA protein expression in SC cells.[128]

7.5.5. Neem. Neem is a natural compound belonging to the family Meliaceae. It is recognized by its botanical name *Azadirachta indica.* It possesses the potential to treat parasitic diseases, skin diseases, oral squamous cell carcinoma, and sexually transmitted diseases and has anti-inflammatory and antibacterial activity.[129,130] Moreover, neem can be used to treat nonmelanoma cells by promoting apoptosis of cancer cells through regulating caspase-3, Bax, caspase-9, and Bcl-2 expression.[131]

7.5.6. Cocoa. Cocoa is obtained from plant seeds *Theobroma cacao* L. of the family Sterculiaceae.[132] Cocoa is a traditional medicine that can be used in the treatment of malaria, worm expellers, and wound healing.[133] The research found that cocoa can decrease the cell viability and cell growth of melanoma cell lines, i.e., B16-F10 and A-375, by inducing oxidative stress in cells.[134]

7.5.7. Myricetin. Myricetin is a naturally occurring component found in various fruits, tea, and wine. Various families like Anacardiaceae, Pinaceae, Primulaceae, Polygonaceae, and Myricaceae are the major sources of myricetin. The study showed that myricetin possesses an anti-inflammatory, antidiabetic, and anticancer effect on colon cancer as well as anti-obesity properties, and it is hepatoprotective.[135] Myricetin also blocks the development of the Cyclin B/CDK1 complex in SC cells. Moreover, myricetin triggers anti-oncogenes (p53) and promotes the expression of CDK inhibitors (p27 and p21), thus restricting the cell division of SC cells.[136]

7.5.8. Silymarin. Silymarin is a obtained from the *Silybum marianum* of the family Asteraceae and is also recognized as milk thistle.[137,138] A study showed that it is a promising molecule that manages various types of disorders including prostate cancer and liver, cardiac, and neurological diseases.[139] The study showed that silymarin protects against skin cancer which is induced due to UVB radiation.[141] Moreover, it induces the repairing of cyclobutane pyrimidine dimers and increases the DNA damage of nonmelanoma SC cells through the up-regulation of p53.[140]

7.5.9. Zyflamend. Zyflamend is an herbal extract derived from turmeric, rosemary, green tea, and ginger. It is used to treat pancreatic cancer and inflammation.[141,142] It promotes caspase-9 cleavage in SC cells. It was also found that zyflamend inhibits angiogenesis, invasion, metastasis, and tumor cell proliferation via regulating inflammatory pathways.[143]

7.5.10. Rutin. Rutin is a flavonoid derived from *Ruta graveolens*, of the family Rutaceae. It is present in apricots, tea, grapefruit seeds, cherries, plums, buckwheat, orange, grapes, and onion.[144] It is a natural compound that consists of various pharmacological activities including antimicrobial, anti-inflammatory, and anticancerous effects on lung, liver, and cervical cancer.[145,146] The potency of rutin is evaluated by the researcher on the SC cell line (A375). They found that rutin causes cell mortality of SC cells via promoting autophagy and apoptosis.[147]

7.5.11. Isoliquiritigenin. Isoliquiritigenin is obtained from *Glycyrrhiza uralensis* of the family Leguminosae.[148] It has various therapeutic benefits like antidiabetic, antivirus, anti-aging, anti-inflammatory, and antioxidative properties. It is also used to treat oral cancer by promoting apoptosis and the arrest of the cell cycle during phase G2.[149] Moreover, it can inhibit the growth of skin cancer cells and promote cell apoptosis. Thus, it is a promising candidate that can inhibit the multiplication of melanoma cells via suppressing miR-301b.[150]

7.5.12. Phloretin. Phloretin is a naturally occurring dihydrochalcone obtained from various vegetables and fruits, mostly found in Manchurian apricots and apple tree leaves.[151] It possesses various therapeutic activities including immunosuppressant, hepatoprotective, antioxidant, cardioprotective, and antidiabetic properties.[152] The study showed that phloretin reduces sunburn which occurs due to UV radiation by suppressing the expression of matrix metalloproteinase-9 and inhibiting thymidine dimer formation. UV radiation is a

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Table 2. Natural Drugs and Their Effects along with a Mechanism for the Treatment of Skin Cancer

sr. no.	compound	effect	mechanism	references
1	saffron	decreases the expression of STAT/JAK circuits	restricts the cell cycle in G0/G1 and inhibits cell propagation	116,117
2	green tea polyphenols	suppresses DNA hypermethylation	blocks tumor growth	121
3	diosmetin	regulates caspase circuits	induces apoptosis	123
4	cantharidin	suppresses MAPK (p38, ERK, and JNK)	down-regulates MMP-2/-9 and uPA protein expression	128
5	neem	regulates caspase-3, Bax, caspase-9, and Bcl-2 expression	promotes apoptosis	131
6	cocoa	induces oxidative stress	decreases the cell viability and cell growth	134
7	myricetin	triggers anti-oncogenes (p53)	restricts the cell division	136
8	silymarin	up-regulation of p53	increases the DNA damage	140
9	zyflamend	initiates caspase-9 cleavage	inhibits angiogenesis, invasion, metastasis, and proliferation	143
10	rutin	promotes autophagy and apoptosis	induces cell mortality	147
11	isoliquiritigenin	inhibits miR-301b	inhibits cell multiplication	150
12	phloretin	suppresses expression of matrix metalloproteinase-9 and inhibits thymidine	-	153
13	apigenin	enhances expression of p53	promotes cell apoptosis	157
14	baicalein	down-regulates MMP-9 and MMP-2 expression	suppresses invasion and migration	160
15	thymoquinone	down-regulates DNMT1	up-regulates BRCA1	162
16	luteolin	inhibits epithelial−mesenchymal transition	blocks the progression of SC cells	170

major cause of SC, thus it is a promising therapeutic target for SC.[153]

7.5.13. Apigenin. Apigenin is obtained from *Teucrium polium* L., *Melissa officinalis*, and *Salvia officinalis* and belongs to the Lamiaceae family.[154,155] It is a traditional herb which is used to treat various types of cancers like prostate cancer, cervical cancer, leukemia, pancreatic cancer, breast cancer, liver cancer, and lung cancer.[156] A current study showed that apigenin decreases the incidence of SC. On the basis of the findings of this study, we concluded that apigenin is a novel lead compound that enhances the expression of the tumor suppressor gene (P53) and promotes cell apoptosis.[157]

7.5.14. Baicalein. Baicalein is a flavonoid obtained from the leaves of *Thymus vulgaris* and *Oroxylum indicum* and the roots of *Scutellaria baicalensis*.[158] In numerous human cancer cells, including melanoma cancer, baicalein has been demonstrated to suppress cell proliferation and trigger apoptosis.[159,160] Nevertheless, baicalein has also been shown to decrease osteosarcoma cell metastasis in vitro and in vivo, along with prostate, lung, breast, and liver tumors.[161] It significantly reduced invasion and migration in B16F10 melanoma cells by inhibiting the activity of MMP-2 and -9. Furthermore, it enhances tight junction strengthening linked with the suppression of claudin expression, which is related to the inactivation of the PI3K/Akt signaling pathway.[160] Current findings suggest that baicalein is a promising therapeutic candidate for melanoma therapy.

7.5.15. Thymoquinone (TQ). TQ is the biologically active constituent found in black cumin (*Nigella sativa*) seeds.[162] Several studies have demonstrated the effectiveness of TQ in treating neoplasms, including skin, ovarian, breast, colon, prostate, liver, and cervical malignancies.[162−164] To sum up, this study's results showed that TQ blocked the β-catenin signaling pathway, which in turn prevented melanogenesis in B16F10 murine melanoma cells, as well as zebrafish melanogenesis. TQ did not appear to be harmful to normal melanocytes, but it was toxic to both of the melanoma cell lines that were investigated.[165] Effective anticancer therapies depend on the production of TQ and TQ-loaded nanocarriers of melanoma cells obtained from various phases of the disease.[166] The results of this investigation could be helpful in the future for developing treatments for melanoma and pigmented lesions.[165]

7.5.16. Luteolin. Luteolin (3′,4′,5,7-tetrahydroxyflavone) is a flavonoid found in large amounts in *Hedyotis diffusa* and *Lonicera japonica*, among many other plants, and has been utilized extensively in the treatment of melanoma.[167] It is widely known that luteolin has antitumor effects on a variety of human cancers.[168] Additionally, it has been observed that luteolin inhibits EMT in cancer cell lines including PC3 and A431.[169] The chemotherapeutic activity of luteolin was evaluated by the researcher on a melanoma cell line (B16F10 cells). By regulating the β3 integrin, luteolin prevents hypoxia-induced EMT in malignant melanoma cells both in vitro and in vivo. This suggests that luteolin could be used as a chemotherapeutic and chemopreventive molecule for melanoma,[172] as shown in Table 2 and Figure 3.

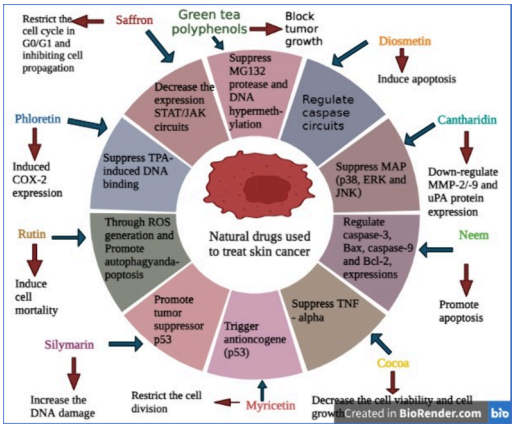

Figure 3. A pie illustration describes the main natural drugs and their mechanism for the treatment of skin cancer (created with BioRender.com).

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Table 3. Compounds and Their Appropriate Ligands and Mechanisms

compound	ligand	mechanism	reference
calcipotriol combined with 5-fluorouracil	TSLP, HLA class II, and NKG2D	increases $CD4^+$ T cell immune response	104
imiquimod	Toll-like receptor (TLR) ligand	promotes apoptosis and autophagic cell morbidity	172
cannabinoids	CB1r/CB2r, TVRPs, PPARs, and GPR55	inhibits angiogenesis and promotes apoptosis	177
5-aminolevulinic acid	folic acid (FA)	produces reactive singlet oxygen ($^1O_2$), which is highly toxic and leads to cell apoptosis or necrosis	178
rosemary	the prototypical ligand 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), indirubin (IND), pityriazepin (PZ), and 6-formylindolo[3,2-*b*] carbazole (FICZ)	promotes intracellular ROS, which induces necrosis	179,180

7.6. Compounds with Their Ligand and Their Mechanism for the Treatment of Skin Cancer. *7.6.1. Calcipotriol Combined with 5-Fluorouracil.* Calcipotriol down-regulates SC. Calcipotriol combined with 5-FU treatment promotes HLA class II, TSLP, and natural killer cell group 2D (NKG2D) expression of ligands in the keratinocytes linked with a marked $CD4^+$ T cell infiltration.[104]

7.6.2. Imiquimod. Imiquimod, which is also called R-837 or S-26308, was first approved by the US Food and Drug Administration (USFDA) for the treatment of anal and genital swellings or warts. Later, it was found that it possesses anticancer activity.[171] Imiquimod is a Toll-like receptor ligand, used to treat different types of cutaneous malignancies.[172] Recently, researchers proved that imiquimod promotes programmed cell death and autophagic cell mortality by inducing mitochondria-mediated apoptosis and ER-stress/PERK/PKR axis via an increasing ROS in SC cells.[173]

7.6.3. Cannabinoids. Cannabinoids are obtained from *Cannabis sativa* L., which is a traditional medical plant belonging to the family Cannabacea.[174,175] Cannabinoids restrict the growth of breast cancer cells and down-regulate the oncogene (cyclooxygenase-2 (COX-2) and c-fos).[176] Moreover, CB2 (CB2R) and GPR55 are the G-protein-coupled receptors overexpressed in tumors and cancer cells.[178] Cannabinoids induce apoptosis and restrict angiogenesis during SC.[177]

7.6.4. Aminolevulinic Acid. Protoporphyrin IX (PphIX), a powerful photosensitizer used in photodynamic therapy, is produced from 5-aminolevulinic acid (5-ALA). Hollow mesoporous silica nanoparticles (HMSNPs) functionalized with folic acid (FA) were prepared to deliver 5-ALA. PphIX can produce reactive singlet oxygen ($^1O_2$), which is extremely toxic and eventually causes cell death or necrosis.[178]

7.6.5. Rosemary. Rosemary is a shrub obtained from *Rosmarinus officinalis* L. of the family Lamiaceae. Rosemary extracted from the leaf promotes intracellular ROS which induces necrosis. It exhibits high antagonist activity against multiple agonists including 6-formylindolo[3,2-*b*] carbazole (FICZ), indirubin (IND), pityriazepin (PZ), and the prototype ligand 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in human keratinocyte cells and in vitro,[179] which is briefly explained in Table 3.

7.7. An Epigenetic Approach for the Management of Melanoma. *7.7.1. Sulforaphane.* Sulforaphane is an isothiocyanate obtained from cruciferous vegetables like broccoli, cauliflower, and cabbage.[181] Researchers found that it inhibits breast cancer metastasis.[182] However, when it is exposed to melanoma cells, it increases nuclear factor 2 (Nrf2) expression and restricts the transformation of cells, NQO-1 (NAD(P)H quinone dehydrogenase 1), and HO-1. The study revealed that its treatment resulted in a decrease in the CpG dinucleotide methylation ratio within the Nrf2 promoter region in melanoma cells. Additionally, sulforaphane inhibited the expression of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) including DNMT1, DNMT3a, DNMT3b, HDAC1, HDAC2, HDAC3, and HDAC4.[182]

7.7.2. Fucoxanthin. Fucoxanthin decreases ROS (reactive oxygen species) levels and promotes apoptosis. It also induces GSH (glutathione) levels via increasing GCLC (glutamate–cysteine ligase catalytic) subunit and GSS (glutathione synthetase) expression by the Akt/Nrf2 pathway in human keratinocyte cells.[183]

7.7.3. Curcumin. Curcumin is obtained from turmeric (*Curcuma longa*), family Zingiberaceae, which has been used for thousands of years for the prevention and treatment of various diseases.[184,185] It can be used to treat several cancers like pancreatic cancer, gastric cancer, hepatic cancer, and colorectal cancer.[186] Moreover, studies showed that curcumin promotes cell cycle arrest at the G1 phase in A375 cells by suppressing cyclin D and phosphorylated retinoblastoma.[187]

7.7.4. Epigallocatechin-3-gallate (EGCG). EGCG is obtained from the leaf of *Camellia sinensis*, family Theaceae.[188] It is a potential therapeutic candidate for the prevention and treatment of cervical and prostate cancer.[189,190] However, EGCG acts as an epigenetic regulator of melanoma, which reduces the expression of DNMTs and inhibits DNA methylation in the SC cell lines SCC-13 and A431.[191] In human SC cells, EGCG has been demonstrated to reactivate important tumor suppressor genes like cip1/p21 and p16INK4a by reducing DNA methylation and increasing histone acetylation.[192]

7.7.5. Mangiferin. Mangiferin is the main constituent obtained from the leaf of *Mangifera indica* L. and belongs to the family Anacardiaceae.[193,194] It has protective effects against various types of cancer including neuronal, breast, colon, and lung cancers via inducing apoptosis.[195,196] Researchers also found that mangiferin has the potential to treat melanoma.[197] It inhibits several NF-kβ target genes during melanoma, like interleukin-6, tumor necrosis factor, interferon-γ, vascular endothelial growth factor receptor 2, matrix metalloprotease-19, and chemokine ligand 2, and inhibits angiogenesis of SC cells,[198] as summarized in Table 4.

7.8. Photodynamic Therapy (PDT) Approach in the Management of Melanoma. PDT is a noninvasive and modern type of therapy utilized for the treatment of various classifications, location of the tumor, and noncancerous ailments. It depends on the photosensitive compound (locally and/or systemic application) collected in pathological cells or tissues.[200] This PS initiates the process of activation by absorbing the radiation of the suitable wavelength and leads to

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Table 4. Drugs, Type of Study, and Their Molecular Mechanism

compound	type of study	molecular mechanism	references
sulforaphane	in vitro	inhibits histone deacetylases and DNA methyltransferase expression	199
fucoxanthin	in vivo	induces GSH and GSS	183
curcumin	in vitro	suppresses cyclin D and phosphorylated retinoblastoma	187
epigallocatechin-3-gallate	in vitro	inhibits DNA methylation	192
mangiferin	-	down-regulates NFkB	198

the selective killing of abnormal cells or tissues. Within the pathological tissues, photoirritative or photocytotoxic reactions take place in the location where the photosensitive compound is dispensed, which permits selective killing.[201] Protoporphyrin-IX-induced PDT is usually utilized in dermatological practices like SC treatment.[202] Treatment of various diseases by utilizing radiation began in ancient times and was used by the Indians, Egyptians, Chinese, and Greeks to treat dermal ailments. In India during the 15th century BC, treatment by utilizing an exogenous compound reacting with the radiation of the sunlight was observed. The mechanism of PDT enables cellular cytotoxicity, and the ROS that is produced promotes autophagy or a necrotic and/or apoptotic approach to cell mortality during the mechanism of PDT.[203] Immunological responses, cellular morphology, enzymatic activity, light intensity and wavelength, oxygen concentration, PS subcellular location, and PS physiochemical features are the aspects that affect the mode and degree of cell mortality.[204] Cell death programmed or nonprogrammed is determined based on these factors.[205] The programmed cell mortality is apoptosis, which is generally characterized by nuclear and membrane destruction.[206] When this type of cell mortality occurs, PSs typically localize in the cellular mitochondria, and it is usually a linked mechanism of cell mortality in PDT.[207] Specific signals activate the apoptosis in target cells that, in response to these signals, activate various pathways leading to suicide.[208] Protein caspases are triggered to destroy cellular contents like polypeptides and nucleic material as the pathways fail.[209] Thus, apoptosis is a controlled and induced process.[210] Nonprogrammed cell death is necrosis and inflammatory responses characterized by it, which are triggered by external stimuli like trauma or infections.[211] The PS that causes necrosis is found in the plasma membranes of target cells. Events in necrotic cell mortality pathways include the motion of calcium ions over the endoplasmic reticulum, lysosomal rupture, cytoplasmic swelling, membrane permeability, breaking down of cell components, calcium-dependent calpain activation, and overall initiation of inflammatory responses.[212] Sometimes, PDT-induced apoptotic cell mortality modes can change into necrosis. Different types of cell mortality in PDT tumor treatments are autophagy, apoptosis, and/or necrosis. During PDT, energy and electrons are transferred.[207] The dose of PS given to target cells is used to excite the PS. This leads the cell to quickly degrade and die compared to apoptotic mortality.[213] A review by Naidoo et al. reported that Dewaele and co-workers have noted in recent studies that later PDT irradiation of specific PSs and another type of cell mortality called autophagy can occur.[207] When a cell tries to heal itself in response to photodamage, it experiences PDT-induced autophagy; though, if failure of response occurs then the cell is signaled for programmed apoptosis. The cell is signaled for programmed apoptosis if this response fails.[214] PSs PDT for cutaneous indications frequently use a topical PS like methyl amino levulinate or 5-aminolevulinic acid, which are protoporphyrin IX precursors.[215] Oral or intravenous PSs are required for visceral tumor treatment, and porfimer sodium is the frequently utilized PS for this indication.[216] Numerous porfimer sodium derivatives have been developed, where the light at 630 nm (red) is absorbed by porfimer sodium and longer wavelengths are absorbed by second-generation agents, giving more energy for the killing of tumors and lowering the photosensitivity of skin.[217] Third-generation agents are attached to carrier molecules like antibodies directed against

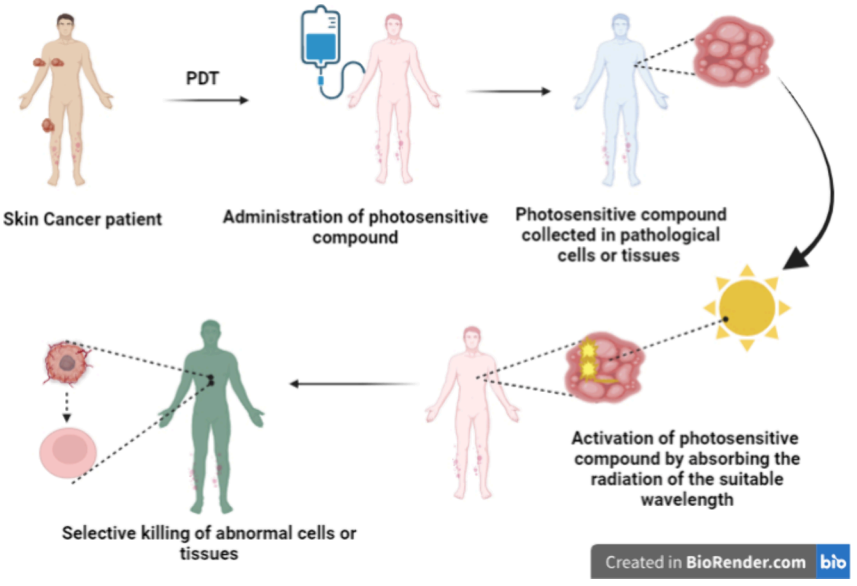

Figure 4. Illustration of the mechanism of photodynamic therapy in the management of skin cancer (created with BioRender.com).

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tumor antigens, liposomes, and other biomolecules that allow the PS to enter the cell or receptor-positive surfaces on tumor cells and allow the PS to accumulate more specifically within the tumor cells, allowing for more precise targeting while sparing healthy tissue.[218] Additionally, endocystic vesicles that release macromolecules into the cytosol through photochemical interfinalization and PSs have been proposed.[219] Only a few PDT sensitizers have received approval from various nations like Japan, the Netherlands, and Canada, in contrast to the US Food and Drug Administration, which has only approved them for a small number of specific indications.[220] PDT has been carried out by a variety of light sources like daylight, lasers, laser-emitting diodes, and incandescent light.[221] The mode of delivery and light characteristics can be changed to target diverse tissue types. Blue light does not penetrate more deeply than red light.[222] Light delivery mode, light exposure time, and the total light dose may be altered. In acute or traditional PDT within a small duration of time, high doses of light are administered; this is not selective and leads to apoptosis of normal neighboring cells or tissue. Acute PDT (aPDT) can lead to pain and a full-thickness skin ulcer that sometimes needs skin grafting or debridement. Additionally, aPDT causes a rapid loss of oxygen, which restricts the synthesis of ROS and consequently the possibility of tumor destruction.[223] Fractionated therapy has similar side effects compared to aPDT but is more effective than single-dose treatments and has, in some instances, permitted clinical relapse and tumor resistance.[222] When using metronomic PDT, light and PSs are administered for a longer duration at low rates or in fractions that are smaller than those of the aPDT fractions earlier mentioned.[224] Although preclinical research is promising, the method has not been applied to human volunteers,[216] as summarized in Figure 4.

7.9. Targeted Therapy for BRAF-Mutated Melanoma. A BRAF mutation is detected in early melanogenesis in a high percentage of melanocytic nevi, hence it cannot induce melanoma progression alone and needs additional genetic alterations at a later stage of progression, such as deletion of phosphatase with tensin homologue (PTEN), autophagy related 5 (ATG5), or cyclin-dependent kinase inhibitor 2A (CDKN2A), to give an advantage in the propagation of melanocytic cells to be transferred to melanoma cells.[225]

Furthermore, BRAF is one of the most frequently mutated oncogenes recognized in melanoma. The most frequent oncogenic BRAF mutations consist of a single point mutation at codon 600 (mostly V600E) that leads to the constitutive activation of the BRAF/MEK/ERK (MAPK) signaling pathway. Therefore, mutated BRAF has become a useful target for molecular therapy and the use of BRAF kinase inhibitors has shown promising results.[226]

However, recent advances in gene sequencing have shown that activated BRAF mutations are present in more than 50% of malignant melanomas and contribute to constitutive signals in the MAPK pathway. Besides the importance of its mutations in cell proliferation, BRAF is associated with lymph nodes and brain and liver metastasis along with the loss of PTEN expression and ATG5. Knowledge of this genetic alteration has led to the development of personalized and targeted therapy strategies which block different pathways, driving melanoma pathogenesis. Several targeted therapy agents such as vemurafenib, dabrafenib, and encorafenib have been approved by the FDA as BRAF inhibitors, as well as other immunotherapies such as anti-CTLA-4 (ipilimumab),[227] which is summarized in Table 5.

Table 5. Targeted Therapy for Melanoma Using BRAF Inhibitors

BRAF inhibitor	targeted chemotherapy generation	current status	references
sorafenib	first-generation inhibitors	FDA approved	225,228,229
LY3009120, BGB659	third-generation inhibitors	under phase I trial	225,230
dabrafenib	second-generation inhibitors	phase I trial	225,231
dabrafenib, trametinib, and spartalizumab (combination therapy)	third-generation inhibitors	under phase III trial	232
nivolumab and ipilimumab	third-generation inhibitors	phase III trial	232,233
vemurafenib	-	approved	226,234
temsirolimus	-	-	5,235

7.10. Nanotechnology-Based Drug Delivery System for Melanoma. Recent decades have seen significant advancements in the field of nanotechnology, particularly in its use in medicine.[236] Due to their distinct abilities to enhance drug delivery, nanoagents offer novel approaches for the treatment of many diseases. These obstacles can be overcome by using nanotechnology to achieve targeted drug delivery, enhance pharmacokinetics, and increase bioavailability.[237] Various types of nanoagents have been utilized in clinical studies for drug delivery, immunotherapy, imaging diagnosis, and vaccine development. However, the full potential of nanotechnology in treating diseases is yet to be realized.[238] Nanocarrier drug delivery systems (DDSs) are among the most important methods of utilizing nanomaterials. These DDSs utilize nanoparticles as carriers to transport active molecules, such as drugs, to the correct target in the body. DDSs are more precise than free drugs and can considerably augment the therapeutic effect of medications while decreasing potential side effects.[239] Melanoma treatment has used many nanosystems such as lipid systems, natural nanosystems, polymeric systems, and inorganic nanoparticles.[240] For example, lipid nanosystems, including liposomes, solid lipid nanoparticles, and nanoemulsions, have been created. Inorganic nanoparticle systems like gold nanoparticles, silica nanoparticles, nanotubes, and copper nanoparticles are also common. Exosomes, which are naturally occurring nanosystems, consist of polymeric micelles, dendritic macromolecules, nanospheres, hydrogels, and polymeric nanoparticles.[240]

7.10.1. Lipid Nanosystems. Lipid systems are highly effective in terms of physical stability, controlled release, and biocompatibility. These systems are also known for their low side effects, biodegradability, and excellent physical stability. They have been extensively researched for their potential in treating clinical diseases. Some examples of lipid systems are liposomes, solid lipid nanoparticles, and nanoemulsions. Among these, liposomes are a type of double nano DDS that has shown great promise in the treatment of cancer due to their favorable pharmacokinetic properties. Studies have also revealed that liposomes can enhance the effectiveness of medications in treating melanoma, especially those that target

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the cell cycle, like paclitaxel. Furthermore, liposomes can significantly prolong the half-life of drugs in circulation.[241]

7.10.2. Nanoparticles. Inorganic nanoparticles, like silver nanoparticles, gold nanoparticles, silica nanoparticles, and nanotubes, have good biocompatibility and enable simultaneous imaging and drug delivery.[242] These nanoparticles, however, frequently need to be combined with other targeting ligands because they may not allow precise targeting of the affected region. One can create gold nanoparticles (1−150 nm) with a variety of geometries, including nanospheres, nanoshells, nanorods, and nanocages.[243] Compared to other biomedical nanotechnologies, these particles possess a distinct set of physical, chemical, optical, and electronic properties. Additionally, they provide a versatile platform for various biochemical applications, including the delivery of genes, imaging agents, and drugs. By linking proteins, DNA, and smaller drug molecules to the surface chemistry of gold nanoparticles, a therapeutic effect has been observed in different types of tumors, including melanoma.[244]

7.10.3. Dendrimers. Dendrimers are unimolecular, monodisperse, synthetic polymers (15 nm) with layered architectures made up of a central core, an internal region made up of repeating units, and different terminal groups that determine the three-dimensional dendrimer characteristic structures.[245] Due to their desirable characteristics, like well-defined size and molecular weight, mono dispersity, multivalency, the quantity of available internal cavities, the high degree of branching, and the abundance of surface functional groups, dendrimers can be prepared for the delivery of both hydrophobic and hydrophilic drugs, nucleic acids, and imaging agents. Numerous academic sources show that dendrimer-targeting ligands can cause the precise targeting and eradication of tumors.[246]

7.10.4. Hydrogels. Hydrogels are 3D (three-dimensional), hydrophilic polymeric networks that can absorb large amounts of water, biological fluids, or molecules. These systems have special qualities that increase the therapeutic agent's effectiveness and reduce unfavorable side effects.[242] Administering anticancer medications topically or through transdermal application using a drug delivery system can reduce side effects and improve the drug's effectiveness. Compared to other methods of drug delivery and traditional therapies, using hydrogels to deliver antiproliferative agents in melanoma SC has numerous benefits.[242] By controlling the structure on a molecular level, including cross-linking density and customizing properties such as biodegradation, degradation rate, pore size, mechanical strength, and chemical and biological responses to stimuli like pH, enzymes, and temperature, polymer engineers can design and create hydrogels. Additionally, the low cost of hydrogels compared to other polymeric formulations like nanoparticles, microparticles, and dendrimers is a significant advantage. Therefore, a hydrogel is a preferred option for melanoma cancer therapy due to its highly adaptable and modifiable characteristics.[243]

7.10.5. Exosomes. Exosomes are nanovesicles comprising various biomolecules. Target cells take up exosomes that are produced by cells during exocytosis. Exosomes can be utilized as natural nano DDSs because of their distinctive properties.[244] Exosomes are double-membraned cellular vesicles that range in size from 30 to 150 nm. Additionally, these vesicles can target particular cells, pass through cell membranes, and carry a variety of biomolecules, such as proteins, lipids, and nucleic acids.[245] Due to their unique pro-tumorigenic characteristic, exosomes may be used as a useful tool in the diagnosis and prognosis of cancer.[246]

8. BIOLOGICAL APPROACHES TO TARGET VALIDATION

The lack of selectivity for the population of regulatory T cells (Tregs) that infiltrate tumors (ti-Tregs) necessitates the need for a ti-Treg-specific biomarker, which causes the modulation and depletion strategies for these cells to have several undesirable side effects.[247] Although antiprogrammed death (PD)-1 (aPD1) therapy is an effective treatment for metastatic melanoma, more than 50% of patients still progress. Researchers tested a first-of-its-kind immune-modulatory vaccine (IO102/IO103) against indoleamine-2,3-dioxygenase (IDO) and PD ligand 1 (PD-L1) to target immunosuppressive cells and tumor cells that express IDO and/or PD-L1. Nivolumab was also tested in amalgamation with the vaccine. The systemic toxicity profile was comparable to that of nivolumab monotherapy, which was the primary outcome, and the project was successful and safe. Efficacy and immunogenicity were secondary end points with 43% (CI, 27.4−60.8%) whole responses, and an objective response rate (ORR) of 80% (CI, 62.7−90.5%) was reached.[248] To reduce toxicities during treatment, targeted therapy has replaced broad-based chemotherapy in current antitumor research initiatives, and new research demonstrates that changed cellular metabolism in tumor cells can be used as new targets for targeted intervention. The changed metabolic functions in cancerous cells and the changed glycosylation are because of their known effects on tumor tumorigenesis, metastasis, and drug resistance. Researchers believe that the enzymes necessary for the synthesis of UDP-hexoses, glycosyl donors for the synthesis of glycans, could be used as tumor therapeutic targets. A drug-like chemical fragment, GAL-012, was discovered via structure-based virtual screening and kinetic assays. It inhibits a small family of UDP-glucose pyrophosphorylase (UGP2), UDP-hexose pyrophosphorylases-galactose pyro-phosphorylase (GALT), and UDP-*N*-acetylglucosamine pyrophosphorylase (AGX1/UAP1) with an IC_{50} of 30 μM. The docking research confirmed that GAL-012 interacted with GALT binding sites at Ser192 and Trp190, UGP2 binding sites at Lys127 and Gly116, and UAP1/AGX1 at Lys407 and Asn327, respectively. GAL-012-2, one of the GAL-012 derivatives, also showed inhibitory activity against GALT and UGP2.[249] Melanoma occurrence is still on the rise, and patients with metastatic melanoma still have poor prognoses. One of the main immune checkpoints is the cytotoxic T-lymphocyte antigen-4 (CTLA-4), which inhibits T cell activation pathways. A novel strategy to combat tumor-induced immune tolerance involves increasing T cell triggering by inhibiting CTLA-4 with an antibody. Early in 2011, the FDA approved ipilimumab after anti-CTLA-4 therapy recently demonstrated significant clinical benefits in patients with metastatic melanoma.[250]

9. FUTURE CHALLENGES OF PDT

Compared to radiation therapy or surgery, PDT is less invasive and side effects are generally mild and do not last long. Based on the therapeutic protocol and PS, adverse effects related to PDT are respiratory insufficiency, anemia, constipation, pleural effusion, fever, edema, erythema, and photosensitivity.[251] It is very challenging to use the photodynamic effect in disseminated metastases with the current technology because

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it only occurs selectively in the irradiated site.[252] Oxygenation of tissue is important for the application of the photodynamic effect, therefore tumors surrounded by dense masses of tumor or necrotic tissue can result in inadequate PDT.[253] When PDT is considered an option for diagnosis, the most crucial factor is the precision of target tissue irradiation. Because of the inadequate penetration of radiation into the tissue, it is difficult to treat deep tumors.[252,254] PDT is a complex treatment that requires accurate planning, which can be done with the aid of computer programs or stimulation.[255]

10. CONCLUSION

SC is becoming a serious public health issue at present and its incidence is increasing worldwide. It occurs due to the involvement of various factors. UV exposure has the greatest impact on the risk of SC. UV rays (UVA and UVB) directly or indirectly damage the DNA and then produce oxidative stress, inflammation, mutation, and immunosuppression. The pathophysiology of SC is very diverse, and for its management, various ligands can be utilized for targeting, like antibodies, nanobodies, peptides, proteins, etc. According to various studies, natural drugs like galangin, phloretin, cantharidin, diosmetin, green tea polyphenols, and saffron are very effective for the treatment of SC at the early stages. Moreover, PDT is a noninvasive and modern type of therapy, utilized for the treatment of various types of cancer, tumor locations, and noncancerous ailments. However, there is a pressing need for effective therapy to cure SC, especially at the advanced stages.

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