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Review Article

Skin cancer therapy: From conventional to nutraceutical based nanovesicular carriers

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ABSTRACT

Skin cancer has one of the highest incidences of any type of cancer with an increasing incidence rate worldwide. It is life-threatening and has led to immense economic and human loss all over the world. The conventional treatment strategies have profound adverse effects, which necessitated the development of novel methods. Nutraceuticals are naturally occurring compounds, and they were reported to exhibit great efficacy in cancer treatment and prevention. Accordingly, topical delivery of nutraceuticals can be considered the most optimum approach for the efficient and safe treatment of skin cancer. However, the utmost challenge to topical drug delivery is the impermeable nature of the skin which hinders drug penetration/permeation. Hence, the use of vesicular delivery systems for nutraceuticals has been a chief research area for years. In this review, we overview skin cancer with its pathogenesis, conventional treatment strategies, and the nano-carrier based approaches for the delivery of nutraceuticals through the skin.

Keywords: *Skin cancer; nutraceuticals; topical delivery; vesicular delivery system; conventional treatment; novel methods.*

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1. Skin Physiology

Skin is the largest organ of our body, acting as a barrier between internal organs and the surrounding. It has many physiological roles; first of all, it acts as the first line of defense against the entry of any foreign body such as chemicals and microorganisms, and it also prevents the loss of fluids and salts from the body. Moreover, it helps in thermoregulation. It consists of three main layers namely from outside to inside; the epidermis, the dermis, and the subcutaneous tissue **[1]**.

1.1. The Epidermis

The epidermis is the outermost layer of the skin that acts as the major blockade and is subdivided into the viable epidermis (VE) (50–100 μm) and the non-viable but chemically active "Stratum Corneum"(SC) (10–15 μm) which is generated from the viable epidermis. The VE is composed of the following layers from inside to outside: Stratum basale or germinativum, Stratum spinosum, and Stratum granulosum. The stratum

basale where melanocytes are found is responsible for producing melanin skin pigment as well as protecting the body from the detrimental effects of UV exposure. Stratum spinosum composed of keratinocytes bound together by desmosomes is responsible for the structural integrity of the skin. Stratum granulosum is composed of flatter keratinocytes and acts as a barrier to fluids such as water **[2]**.

Keratinocytes which represent the majority of the epidermal cells migrate from the VE towards the skin surface, during which they undergo differentiation and maturation leading to obvious structural amendments forming the corneocytes. Corneocytes are flat dead cells containing high amounts of keratin filaments and water and surrounded by a hydrophobic matrix composed of keratin, ceramides, cholesterol, cholesterol esters, and fatty acids. Moreover, corneocytes are interconnected by specialized junctions, named corneodesmosomes. The "bricks and mortar" model is used to exemplify the SC, where the bricks are the corneocytes implanted in a mortar whose surrounding matrix consists of ceramides, cholesterol and cholesterol esters, as well as fatty acids. The complexity of SC led to considering this layer as the limiting factor for drug penetration across the skin **[3]**.

1.2. The Dermis

It is a hydrophilic layer rich in blood capillaries and is composed of a dense network of fibers (collagen and elastin) providing mechanical strength to the skin besides its nutritious role. Any substance reaching it can pass into the systemic circulation. It is divided into the papillary dermis and reticulate dermis. The papillary dermis is a thin layer composed of lightly arranged collagen while the reticulate dermis is a thick layer composed of subcutaneous fat. The main cells in the dermis layer are fibroblasts, mast cells, and macrophages **[2]**.

1.3. The Subcutaneous tissue (hypodermis)

This tissue comprises 10% of the total body weight of healthy individuals and has multiple fundamental roles which are thermal regulation, insulation, energy provision, and protection of the body against mechanical injuries **[2]**.

The complicated physiology of the skin is the major obstacle for topical delivery. The other obstacles are the characteristics of the drug such as molecular weight, degree of ionization, partition coefficient, diffusion coefficient, and physicochemical nature of the drug. Drugs should have a molecular weight of less than 500 Dalton (Da). The characteristics of the vehicle and diffusion of the drug are also important in controlling the permeation of the drug across the skin **[2]**.

2. Skin cancer

Skin cancer is the most commonly recognized malignancy in the US **[4]** and has led to immense economic and human loss all over the world **[5]**. The incidence of skin cancer in Egypt is quite less than in the US, however, it is still high **[6]**.

Skin cancers are categorized to the cell from which they arise and their clinical behavior and are generally divided into melanoma which is caused by the malignant transformation of melanocytes and non-melanoma which is derived from the epidermal cells **[7]**. These groups represent 95% of skin cancers with other types of cutaneous malignancies representing a minor percentage **[7]**. Types of skin cancer are shown in **Fig. 1.**

Non-melanoma skin cancer (NMSC) is subdivided into common keratinocyte carcinomas and rare neoplasm. Common keratinocyte carcinomas are Basal cell carcinoma (BCC) originating from the basal layer of the epidermis and squamous cell carcinoma (SCC) originating from the spinous layer **[7]**. They both share cellular lineage with keratinocytes. They are the

most common malignancies worldwide with an annual incidence that beats the other malignancies collectively. Other rare types of skin cancer include Merkel cell carcinoma (MCC) and cutaneous sarcomas **[7]**. NMSC causes many deaths worldwide annually despite having an immense cure rate. Moreover, it causes a higher degree of impairment as measured by the Disability-Adjusted Life Years (DALY) than melanoma **[8]**.

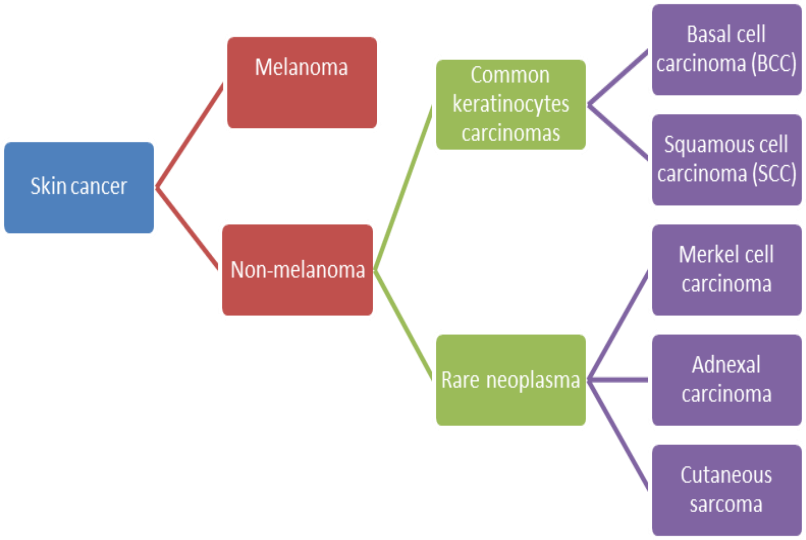

Fig. 1. Diagrammatic presentation for types of skin cancer

Melanoma skin cancer develops from melanocytes found at the bottom of the epidermis which protects the skin from being exposed to external environmental factors. It is less common among the different types of cutaneous malignancies but is associated with poor prognosis making it the most lethal. It rarely occurs in mucosal surfaces such as GIT, genital mucosa, and oral cavity with a mortality rate of 90% and a survival rate of fewer than 10 years when metastasized **[9]**. Melanoma has the highest rate of metastatic effect, once located in the dermis it spreads to other sites through the lymphatic system and bloodstream **[9]**. Hence, melanoma is considered a significant health threat.

2.1. Pathogenesis of skin cancer

UV radiation is considered the chief risk factor for keratinocyte carcinoma (KC), thus, keratinocyte carcinoma is classified as an occupational disease for outdoor jobs **[8]**. UV radiation is mainly composed of UVA of wavelength (320-400 nm) and UVB of wavelength (290-320 nm). Both UVA and UVB are oncogenic but because UVB is absorbed by the skin, it's considered more carcinogenic than UVA. UVB causes direct damage to DNA and RNA *via* prompting the formation of a covalent bond between adjacent pyrimidines, leading to the formation of mutagenic photoproducts as cyclopyrimidine dimers and pyrimidine-pyrimidine adducts which cause mutation of tumor suppressor genes **[10]**. UVB exposure activates the signal transduction molecule protein C kinase and is implicated in the formation of reactive oxygen species (ROS) through the photo-oxidative-stress-mediated mechanism. Moreover, it impairs the role of tumor suppressor T-cells, consequently causing tumor development and failure in immune response **[10]**. UV

radiation exposure also causes inactivation of the TP_{53} tumor suppressor gene which plays a major role in the induction of NMSC and mutation of transcription factor P_{53}, which renders cells resistant to apoptosis, leading to clonal expansion of precancerous keratinocytes. Approximately 90% of squamous cells and 50% of basal cell carcinomas have this mutation [10]. Cumulative sun exposure also causes UV-induced DNA damage leading to SCC. On the other hand, BCC is mainly caused by aggressive intermittent exposure. Additionally, exposure during childhood leads to the development of BCC rather than SCC **[10]**. Interestingly, there is gender bias in skin cancer, with males showing a twofold greater incidence of NMSC upon UV exposure which is attributed to the decreased catalase activity in males vs females **[11]**.

Recently, it has been reported that there is a link between KC and human papillomavirus (HPV) because HPV DNA can be detected in up to 90% of all KC in immunocompromised patients and up to 50% in immunocompetent patients **[8]**. Xerodermapigmentosa is a rare autosomal recessive disorder of DNA repair in which the ability to repair damage caused by UV radiation is impaired. Those patients are subjected to increased childhood skin malignancies **[7]**.

2.2. Conventional treatment of skin cancer

2.2.1. Treatment of non-melanoma skin cancer

A. Cryosurgery or Cryotherapy

Cryosurgery is an insignificantly invasive and effective treatment method for certain tumor ablation. It is a technique that uses subzero temperatures produced by the cryogenic agent which lowers the temperature of the targeted tissue under its cold-resistance threshold and crystallizes the tumor cells causing necrosis and tissue destruction **[12]**. Common local reactions include: pain, blistering, delayed wound healing, alopecia, permanent hypopigmentation. Rare adverse reactions include hypertrophic scarring, tissue distortion, and severe painful hemorrhagic bullae **[12]**.

B. Topical therapies

Worth mentioning is that in the topical treatment of skin cancer the main goal is drug permeation and retention in the epidermis which requires specific drug properties such as; molecular weight less than 500 Da, drug should be in the unionized form at skin pH, and adequate lipophilicity **[13]**. To limit the systemic (transdermal) delivery of drugs and allow for high deposition of drugs in the skin, it can be postulated that the higher the molecular weight and log P values of drugs the higher their possibility of depositing in skin layers. Listed below are the only FDA approved drugs for topical treatment of skin cancer:

5-Fluorouracil (5-FU)

5-FU received FDA approval for the treatment of non-melanoma skin cancer in the 1970s **[14]**. It's an antineoplastic antimetabolite pyrimidine analog that inhibits thymidylate synthase; the rate-limiting enzyme in the pyrimidine nucleotide synthesis. Consequently, this thymine deficiency interferes with DNA and RNA synthesis which are essential for cell division and growth. This deficiency stops the growth of rapidly proliferating or cancerous cells leading to cell cycle arrest and apoptosis **[14]**. Common local adverse reactions are pain, crusting, erythema, dermatitis, pruritis as well as secondary infections causing discontinuation of treatment course **[12]**.

Imiquimod

Imiquimod received FDA approval for the treatment of non-melanoma skin cancer in 2004 **[14]**. It’s a Toll-like receptor 7 agonist that potently stimulates the innate and cell-mediated immune responses **[12]**. It upregulates a variety

of pro-inflammatory cytokines leading to the production of interferon by CD4 cells which stimulates cytotoxic T cells leading to apoptosis **[12]**, **[14]**. Local reactions are similar to those of 5-FU **[12]**.

Ingenolmebutate

Ingenolmebutate received FDA approval for the treatment of non-melanoma skin cancer in 2012 **[14]**. It's a plant extract with a dual mechanism of action, the first of which is promoting rapid lesion necrosis *via* mitochondrial swelling and membrane disruption. Secondly, the activation of protein C kinase contributes to the destruction of cancerous cells and the avoidance of relapse **[12]**, **[14]**. Local reactions include erythema, pain, and edema **[12]**. The complete and partial clearance rates were reported to be 37% and 60% respectively **[14]**.

Other non-FDA approved therapies are also present in literature**[15]**–**[17]**; diclofenac, topical retinoids, resiquimod, piroxicam, mechlorethamine HCl, carmustine, potent glucocorticoids, betulinic acid, calcium besylate, and potassium dobesilate containing formulations.

C. Photodynamic therapy (PDT)

Photodynamic therapy is an FDA approved non-invasive light-based therapy for the treatment of NMSC **[8]**, **[12]**. It's a two-step procedure including first the topical or systemic administration of a photosensitizer such as a methyl aminolevulinate and 5-aminolevulinic acid, which is quickly uptaken by keratinocytes and converted to porphyrin IX, then, the sensitized tumor is subjected to a light source from the blue or red spectrum in the presence of oxygen. The illumination causes the production of reactive oxygen species, particularly singlet oxygen, leading to cell death *via* apoptosis or necrosis, hence promoting the destruction of the tumor **[7]**, **[12]**. Owing to the deeper tissue penetration, red light is mainly used for cutaneous cancers **[12]**. Unfortunately, PDT has high lesional recurrence (14%) and low clearance rates (76%). Adverse effects reported are classified into those encountered during treatment such as burning or stinging pain requiring the administration of analgesics, and post-treatment adverse effects such as erythema, edema, inflammation, hypo or hyperpigmentation **[12]**.

D. Radiation therapy (RT)

Radiation can be used to treat NMSC. There are several types of radiation including megavoltage electron beam, orthovoltage, superficial x-ray radiation **[12]**. The choice of method depends on the target area. In the case of primary superficial tumors, the three types can be used with orthovoltage reporting 10-20% higher relative effectiveness in comparison with electron and photon energies. The advantages of these methods for lesions less than 1 cm deep are sparing healthy tissue as the less lateral margin of the normal tissue is exposed, moreover ensuring maximum dose at skin surface **[18]**. Recently, electrons have been widely used for lesions of up to 4cm depth, however, for lesions of depth more than 5 cm, photon beams are used together with electrons or photon intensity-modulated radiotherapy **[18]**. Radiation therapy was reported to achieve clearance rates for BCC more than 90% **[12]**, **[18]**. However, in the case of SCC increased risk of failure, earlier recurrence and higher levels of death have been reported **[12]**. Moreover, radiation therapy is accused of damaging rapidly dividing epithelial cells of skin and mucosa which begin to recover within 14 to 21 days after RT completion owing to the movement of surviving stem cells from the basal layer to the surface. Erythema, desquamation, edema, and hair loss are commonly reported acute toxicities. Besides, patients should have lifestyle amendments such as avoiding shaving, sun exposure, use of creams, perfumes, and

aggressive cleaners during and after RT. On the other hand, the steroid cream may reduce irritating symptoms **[12]**, **[18]**.

2.2.2. Treatment of melanoma skin cancer

Melanoma is the most aggressive type of skin cancer owing to its multidrug resistance, low survival rate, and high frequency of relapse **[19]**. It is reported that early detection of melanoma is a necessity where surgical removal of the tumor is applicable offering a 99% survival rate **[19]**. Surgery was reported as a treatment option for melanoma **[19]**, in addition to two orally administered FDA approved drugs Cobimetinib and Trametinib which block the activity of abnormal proteins that send signals to cancer cells to reproduce as well as slowing down or stopping metastasis, in addition to BRAF inhibitors (Dabrafenib and Vemurafenib), and immunostimulants such as the intravenously administered FDA approved drug Ipilimumab, which binds to the T-lymphocyte-associated antigen 4 (CTLA4), hence preventing the downregulation of the immune system. However, most patients develop drug resistance a few months after starting treatment **[19]**.

The abovementioned drawbacks of conventional treatments of skin cancer highlight the necessity of developing safer treatment alternatives, such as using therapeutic molecules of natural origin.

2.3. Nutraceuticals and their use in skin cancer

Nutraceuticals are dietary components that exhibit not only nutritional value along but also medicinal properties; they possess diverse mechanisms of action in cancer treatment or prevention **[20]**. However, most of the phytochemicals' activity against cancer is related to either their apoptotic activity or antioxidant property **[20]**, **[21]**. Apoptosis is a self-defense tool by which the body gets rid of dysfunctional cells such as metastatic malignant cells without causing secondary oxidative stress. It's worth mentioning that any defect in apoptosis is the major cause of malignancy rather than proliferation dysregulation **[21]**. Cancerous cells acquire apoptotic resistance by either overexpression of anti-apoptotic proteins such as Bc1-2, IAPs, and FLIP or downregulation of pro-apoptotic proteins such as Bax, Apaf-1, and caspase8. Regarding their antioxidant property, most nutraceuticals are polyphenolic compounds, accordingly, their phenolic groups can accept an electron and form phenoxyl radicals which are more stable disrupting oxidation reaction within cells and hence decrease oxidative damage to DNA **[20]**. Other mechanisms of action for nutraceuticals against cancer may include direct alteration of the endocrine system, anti-inflammatory activity, or even a direct effect on DNA repair **[20]**.

The use of nutraceuticals in clinical practice is an evolving research area and will continue to appeal owing to their compatibility with today's lifestyle as well as immense health benefits.

Plant-derived nutraceuticals have demonstrated strong anti-tumor efficacy against skin cancer. Examples for those nutraceuticals are listed below.

2.3.1. Curcumin

The major active constituent of turmeric has been widely studied for about half a decade for its efficacy against many diseases and has gained great attention for its activity against various types of cancers **[20]**, **[22]**. The mechanisms of action of curcumin against tumors include (i) downregulation of anti-apoptotic proteins with subsequent induction of tumor cells apoptosis as well as upregulation of tumor suppressor genes (e.g. p53) **[23]**, (ii) downregulation of matrix metalloproteinases (MMPs),hence prevention of tumor invasion **[24]**. (iii) the anti-inflammatory effect that augments its activity against tumors **[25]**.

2.3.2. Quercetin

It's a common flavonoid with potent anti-inflammatory and anti-oxidative properties and consequently anti-carcinogenic activity **[20]**. It's worth mentioning that the major source of quercetin glycosides is onion **[26]**. Quercetin chemopreventive activity has been an interesting research area for years **[21]**. The mechanism of action of quercetin against cancer includes (i) downregulation of insulin-like growth factor (IGF)-1 signaling **[26]**. (ii) strong antioxidant property owing to the presence of a large number of hydroxyl groups and consequently perfect free radical scavenging, (iii) exhibition of pro-apoptotic effect on tumor cells **[26]**.

2.3.3. Resveratrol

It is a polyphenolic stilbene found abundantly in grapes, berries, peanuts, and red wine **[27]**. It has potent anti-inflammatory and antioxidant effects as well as a high ability to inhibit the progression of various types of cancer cells **[27]**. Its chemopreventive and therapeutic activity against skin cancer is suggested to be due to : (i) antioxidant properties **[27]**, (ii)alterations in the expression and function of Survivin, a member of the inhibitors of apoptosis (IAP) gene **[27]**. It proved its efficacy against both melanoma and non-melanoma skin cancers in in-vivo animal models **[27]**. Moreover, widespread data on human cell lines confirmed that resveratrol can alter many pathways involved in cell growth, apoptosis, and inflammation **[27]**.

2.3.4. Epigallocatechin Gallate (EGCG)

It's the most potent tea polyphenol that is found abundantly in green tea. EGCG has been widely investigated as it possesses preventive and therapeutic effect against skin cancer by multiple mechanisms: (i) inhibits lipid peroxidation and consequently limit DNA damage caused by UV exposure, (ii) reduces the amount of ROS produced by the skin, (iii) exhibits anti-inflammatory property through downregulation of pro-inflammatory cytokines, (iv) can cause cell cycle arrest **[23]**.

2.3.5. Caffeic acidphenethyl ester

It is derived from honeybee propolis. Caffeic acid and its ester derivatives have powerful antioxidant and anti-inflammatory agents that block tumorigenesis **[21]**. Several studies suggest that caffeic acid and its derivatives primarily phenethyl ester inhibit skin carcinogenesis **[28]**. It's cytotoxicity is attributed to: (i) induction of apoptosis **[28]**, (ii) anti-proliferative activity **[28]**, (iii) inhibition of expression of key proteins **[28]**.

2.3.6. Genistein

Isoflavone obtained from soybeans that exhibit strong antioxidant and anti-carcinogenic activity in the skin, protection against photodamage in mice, and inhibit skin carcinogenesis **[22]**. The activity of genistein against skin cancer has been an interesting research area since the 1990s and is suggested to be mainly attributed to its (i)antioxidant property **[22]**, (ii)anti-inflammatory property **[22]**.

2.3.7. Carnosol

It is extracted from rosemary and sage with anti-inflammatory, anti-oxidant, and anti-cancer properties **[29]**. Carnosol has been suggested to have a chemoprotective effect against UVB-induced carcinogenesis by (i) decreasing ROS elevation, (ii) inhibiting the activation of NF-κB by UVB **[29]**.

2.3.8. Garlic

Sulfur metabolites in garlic oil exhibit anticancer activity against many cancer types with diallyl trisulfide (DATS) being the most potent sulfur metabolite against skin cancer **[30]**, **[31]**. DATS possess such activity via boosting immunity and (i) increasing ROS within cancerous cells causing DNA damage, (ii)

mitochondrial-mediated apoptosis, (iii) endoplasmic reticulum stress **[31]**, (iv) downregulation of lipid peroxidation **[32]**, (v) downregulation of COX-2 **[31]**, **[33]**.

2.3.9. 6- gingerol

It is one of the most abundant phenolic ketones in ginger, that induces apoptosis in skin cancer cell lines via; (i) generation of reactive oxygen species (ROS) which reduce mitochondrial membrane potential (MMP), (ii) release of cytochrome C causing the upregulation of apoptotic protease activating factor-1(Apaf-1) **[34]**.

3. Nano- carrier-based approaches for the delivery of nutraceuticals through the skin

The impermeable physiology of the skin is the greatest challenge to topical drug delivery. Thus, designing a formulation that ensures adequate drug penetration and localization within the skin has been an important area of research for years. Many of the conventional dermal vehicles utilize potent physical and chemical enhancers to achieve the aforementioned goal. Physical enhancers act by causing temporary disruption of skin barrier function integrity by microneedles, sonophoresis, laser, thermal ablation, magnetophoresis, and are considered invasive as they may lead to long term disruption to skin barrier properties **[35]**. Chemical enhancers as surfactants, esters, and fatty acids act by perturbing the densely packed SC and solubilizing and extracting keratin or lipid **[35]**, **[36]**. Yet, chemical enhancers have multiple disadvantages, such as the necessity of their use at high concentrations **[37]**, the ability to induce skin irritation **[38]**, leading to toxicity of keratinocytes at certain instances **[39]**.

Thus, as a substitute, the use of nanotechnology has been explored by researchers to overcome the challenges of conventional topical delivery. Nanoparticles are minute substances of dimensions ranging from 1 to 100 nm with unique physical and chemical characteristics because of their large surface area and tiny size **[40]**. They can modify permeation of the encapsulated substances by increasing the solubility of drugs, shielding the drug from physical or chemical instability, providing controlled drug release as well as prolonged contact time with the skin **[35]**, **[41–43]**. It has been suggested by researchers that nanoparticles favorably utilize the hair follicle and intercellular routes of penetration **[44]**, however, all permeation mechanisms are possible. Since the main concern in cancer treatment is targeting, different targeting strategies can be adopted **[45]**; Passive targeting is possible by the tumors leaky vasculature as well as defective lymphatic drainage, which offer enhanced permeability and retention effect (EPR) for antitumor drugs, and active targeting which makes use of another characteristic feature of tumors rather than EPR which is the overexpression of surface receptors. Thus, nanoparticles can be engineered with surface ligands capable of binding to those receptors and cellular internalization takes place by endocytosis. Targeting by vesicular systems is mainly achieved via this method.

Quite a lot of nanoparticle technologies have been described in the literature for dermal drug delivery; these include vesicular systems such as liposomes, transfersomes, ethosomes and penetration enhancer-containing vesicles, lipid nanoparticles such as solid lipid nanoparticles and nanostructured lipid carriers, polymeric micelles, polymeric nanoparticles, nanoemulsions, nanofibers, and metallic nanoparticles. Worth mentioning is that vesicular systems are the most frequently utilized systems to accomplish this purpose **[41]**, **[46–48]**.

Liposomes are globular lipid bilayer vesicles with a size range of 50–1000 nm, which were discovered as drug delivery systems by Bangham

in 1965 **[49]**. Being composed of an aqueous core and lipophilic bilayer, this allows for the encapsulation of both lipophilic and hydrophilic molecules **[50]**. Liposomes have several proposed topical applications **[51]** owing to the following advantages: biocompatibility, improved skin penetration, better therapeutic efficacy, less adverse effects, controlled release, and cell-membrane like structure **[52**, **53]**.

Liposomes use is considered a promising approach to enhance nutraceuticals bioavailability and shelf-life. It was reported that liposomes are efficient carriers for delivery of three vitamins with different solubility; B_{12}, a-tocopherol, and ergocalciferol with enhanced encapsulation efficiency and stability, these vitamins possess strong antioxidant activity **[54]**. Another study revealed that liposomes are effective delivery systems for resveratrol with enhanced entrapment efficiency, improved stability, reduced cytotoxicity in comparison with resveratrol solution of the same concentration, and most notably the preservation of its antioxidant activity **[55]**. Moreover, a study on the antioxidant activity of lycopene upon its incorporation in liposomes was found to enhance its biological activity as well as bioavailability **[56]**. Furthermore, a study was carried out for the incorporation of three diverse flavonoids in liposomes, suggesting that liposomes can be considered as a chief delivery system for flavonoids **[57]**.

The use of liposomes for cancer therapy has been reported for years **[50]**, **[58]** owing to their aforementioned advantages, as well as their ability to increase the localization of anticancer agents in solid tumors by passive targeting **[58]**. Moreover, the topical administration of liposomes encapsulating anticancer drugs has been studied **[59**, **60]**, and it was shown to be devoid of the adverse effects of other treatment strategies, with enhanced patient compliance and reduced treatment cost **[61]**. Among the nutraceuticals encapsulated in liposomes for skin cancer treatment, liposomal curcumin was found to be effective against head and neck squamous cell carcinoma **[62]**. Yet, conventional vesicular systems such as liposomes cannot penetrate deeply into the skin, but rather accumulate in the SC, leading to inefficient drug delivery **[63–65]**. This led to the development of flexible liposomes, which are biocompatible vesicles with ultra-deformability due to the presence of surfactants (e.g. edge activators) that enable them to pass across the skin and transport drugs to deeper layers in comparison with conventional liposomes **[66**, **67]**.

Recently, several types of ultra-deformable vesicles (UDVs) have been studied, whiletransferosomes, ethosomes, penetration enhancer-containing vesicles (PEVs), and transethosomes are the most frequently investigated. Studies revealed that the incorporation of penetration enhancers (PE) in UDVs improved drug transport by penetrating the stratum corneum, owing to the synergic effect of vesicles and PE **[68–72]**.

Transfersomes are lipid-based vesicles that differ from liposomes in being more elastic and ultra-deformable **[73]**. Phosphatidylcholine is the commonly used lipid in transfersomes because it is the most abundant constituent of the cell membrane and consequently, it is well-tolerated by the skin, hence reducing the risk of undesirable adverse effects **[73]**. Transfersomes also contain bilayer softening constituent; edge activators (EA) such as sodium deoxycholate, tween 80, and span 80, responsible for their elasticity **[74]**. This EA produces a high radius of curvature, hence destabilizing the lipid bilayer and enhancing membrane deformability. This enables transfersomes to squeeze across skin layers, and prevents vesicle rupture, and thus transports high drug concentrations in the deep

skin layers **[36]**, **[75]**, **[76]**.

Recently, transfersomes have been widely used for the topical delivery of nutraceuticals. Transfersomes containing epigallocatechin-3-gallate (EGCG) and hyaluronic acid (HA) were prepared to study their synergistic protective ability against UV radiation skin damage, as well as antioxidant and anti-aging effect **[77]**. This study proved that EGCG transfersomes exhibited enhanced skin permeation of EGCG compared to plain EGCG, and they were proven to be promising constituents in sunscreen creams to enhance UV protection, antioxidant and anti-aging effects. Another study of transfersomes encapsulating curcumin revealed that transfersomes exhibited enhanced permeability through the skin when compared to the conventional formulation and hence, exhibited improved anti-inflammatory activity **[78–80]**. A similar study for capsaicin-loaded transfersomes confirmed that transfersomes exhibit improved skin permeation compared to pure capsaicin **[81]**.

Regarding their application in the treatment of skin cancer, apigenin-loaded transfersomes were studied for their skin cancer treatment potential **[82]**. This study revealed that transfersomesloaded with apigenin had high entrapment efficiency, suitable particle size for skin penetration as well as initial burst release followed by sustained drug release. Thus, transfersomes are considered a good carrier for drug delivery across skin layers and consequently skin cancer treatment.

Another UDV is ethosomes, which are soft, malleable vesicles capable of delivering drugs to deep skin layers as well as systemic circulation **[83]**. Ethosomes are composed of phospholipids, high ethanol concentration, and water. The high ethanol concentration is responsible for fluidizing the skin lipid bilayer structure and consequently, when incorporated into a vesicle it improves the vesicles' permeability across the SC **[83**, **84]**.

Ethosomes have been used as carriers for topical delivery of nutraceuticals over the past few years. Ethosomes loaded with ammonium glycyrrhizinate were prepared, and results showed that ethosomal vesicles exhibited superior bioavailability when compared with an ethanolic solution of the drug, with no toxicity **[85]**. Another study has been carried out on apigenin which has antioxidant, anti-inflammatory properties and is expected to have an anti-cancer effect, however, its physicochemical properties lead to reduced bioavailability **[86]**. Ethosomes loaded with apigenin for topical delivery showed enhanced permeability as well as a superior anti-inflammatory effect **[86]**. The use of ethosomes for delivery of curcumin for the treatment of melanoma was found to have great potential for delivering curcumin to the deep skin layers and hence, it was promising in skin cancer treatment **[87]**.

Another UDV is penetration enhancer vesicles (PEVs) **[68]**, **[88]**. PEVs are vesicles comprising a water-miscible penetration enhancer along with phospholipids **[69]**, thus combining the advantage of liposomes as drug carriers as well as the ability of penetration enhancer to impart flexibility and deformability and hence enhancing drug deposition into different skin layers **[89]**.

A study was carried out on sorbitol-PEVs loaded with baicalin, and revealed that baicalin-PEVs exhibited enhanced skin deposition of this flavonoid in the skin as well as skin protection against oxidative stress and UV damage **[90]**. A comparative study of quercetin-loaded PEVs with four different penetration enhancersconfirmed that penetration enhancers augmented the effect of phospholipids in disturbing the stratum corneum, and in penetrating the different skin layers as well as systemic circulation **[91]**. Also, a study for encapsulating epigallocatechin-3-gallate in PEVs for treatment and prevention of

skin cancer combined both the advantages of topical drug application as well as the use of nutraceuticals for treatment of skin cancer. Results showed superior drug delivery as well as efficacy and safety, confirming that this system has great potential for the treatment of skin cancer **[4]**.

Conclusion

Skin cancer has one of the highest incidence rates compared to other types of cancer, and this rate is currently increasing worldwide, probably due to ozone depletion and the accompanying increase in the ultraviolet radiation reaching the Earth. Several conventional treatment strategies are available for skin cancer including surgery, photodynamic therapy, radiation as well as chemotherapy, and immunotherapy; however, they are toxic, costly, and in some cases ineffective. Thus, combining the use of nanotechnology and nutraceuticals has been widely studied as an attractive and safe alternative owing to its ability to deliver drugs via multiple pathways and through various routes of administration, offering efficient drug delivery with fewer side effects.

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article in the main manuscript.

Competing interests

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List of abbreviations

VE, Viable Epidermis; SC, Stratum Corneum; UV, Ultraviolet radiation; Da, Dalton; NMSC, Non-melanoma skin cancer; BCC, Basal cell carcinoma; SCC, Squamous cell carcinoma; MCC, Merkel cell carcinoma; DALY, Disability-Adjusted Life Years; KC, Keratinocyte carcinoma; ROS, Reactive oxygen species; HPV, Human papillomavirus; 5-FU, 5- fluorouracil; DNA, Deoxyribonucleic acid; RNA, Ribonucleic acid; PDT, Photodynamic therapy; RT, Radiation therapy; $CTLA_{4,}$ T-lymphocyte- associated antigen 4; Bc1-2, B-cell lymphoma-2 gene; Bax, Bcl-2-associated X protein; Apaf-1, Apoptotic protease- activating; factor-1; MMP, Matrix metalloproteinase; IGF-1, insulin-like growth factor-1; EGCG, Epigallocatechin; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; DATs, Diallyltrisulfide; COX, Cyclooxygenase; UDVs, Ultra-deformable vesicle; PEVs, Penetration enhancer containing vesicles; PE, Penetration enhancer; EA, Edge activator; HA, Hyaluronic acid;

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