Review Article

Shaloam Dasari, Clement G. Yedjou, Robert T. Brodell, Allison R. Cruse, and Paul B. Tchounwou*

Therapeutic strategies and potential implications of silver nanoparticles in the management of skin cancer

https://doi.org/10.1515/ntrev-2020-0117
received October 30, 2020; accepted December 22, 2020

Abstract: Skin cancer (SC) is the most common carcinoma affecting 3 million people annually in the United States and millions of people worldwide. It is classified as melanoma SC (MSC) and non-melanoma SC (NMSC). NMSC represents approximately 80% of SC and includes squamous cell carcinoma and basal cell carcinoma. MSC, however, has a higher mortality rate than SC because of its ability to metastasize. SC is a major health problem in the United States with significant morbidity and mortality in the Caucasian population. Treatment options for SC include cryotherapy, excisional surgery, Mohs surgery, curettage and electrodesiccation, radiation therapy, photodynamic therapy, immunotherapy, and chemotherapy. Treatment is chosen based on the type of SC and the potential for side effects. Novel targeted therapies are being used with increased frequency for large tumors and for metastatic disease. A scoping literature search on PubMed, Google Scholar, and Cancer Registry websites revealed that traditional chemotherapeutic drugs have little effect against SC after the cancer has metastasized. Following an overview of SC biology, epidemiology, and treatment options, this review focuses on the mechanisms of advanced technologies that use silver nanoparticles in SC treatment regimens.

Keywords: skin cancer, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, biology, epidemiology, clinical manifestations, treatment, silver nanoparticles

1 Introduction

Skin cancer (SC) incidence has been rapidly increasing in the United States for the past three decades. It occurs in individuals with fair skin living in warm and sunny climates [1]. Based on cell biology and clinical behavior, SC is classified as melanoma SC (MSC) and non-melanoma SC (NMSC), which is further delineated into basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) [2]. MSC is the most aggressive form of SC [3]. Risk factors of melanoma include intermittent exposure to sunlight, light color of the skin, and geographical location, although one form, acral lentiginous melanoma, occurs in dark-skinned individuals on the hands and feet [4]. Intense exposure to ultraviolet (UV) rays over an extended period of time is the most important modifiable risk factor in the development of NMSC, although ozone depletion, genetics, and immunosuppression may play a role [5]. Indoor tanning is also associated with a significantly increased risk of NMSC and possibly melanoma with a higher risk when below 25 years of age [6]. It is estimated that over 1,000,000 new cases of MSC will be diagnosed in the United States (US) in 2020 and 6,850 people will die from the disease [7]. Early detection of SC minimizes the risk and increases the potential for effective treatment options.

The effectiveness of SC treatment options and prognosis depend on the type of SC, location, size, and subtype of cancer, and the presence or absence of metastases. Treatment options include excisional surgery, topical chemotherapy, radiation therapy, photodynamic therapy (PDT),
cryotherapy, targeted therapy, and use of immune response modifiers. Risks and benefits must always be considered. Non-targeted chemotherapy for advanced SC is associated with a variety of organ toxicities. This set the stage for the development of novel targeted therapies. This article summarizes the biology, epidemiology, clinical manifestations, treatment strategies, and therapeutic implications of AgNPs in the management of SC.

2 Methods

A scoping literature search was conducted on PubMed, Google Scholar, and Cancer Registry websites focused on the diagnosis and treatment of SC. Key search terms included “skin cancer, melanoma skin cancer, non-melanoma skin cancer, squamous cell carcinoma, basal cell carcinoma, skin cancer diagnosis, skin cancer prevention, and skin cancer treatment, and silver nanoparticles.” The collected data provided invaluable information about the biology, epidemiology, clinical manifestations, treatment strategies, and therapeutic implications of AgNPs in the management of SC.

3 Results and discussions

SC is the most common form of cancer. It affects millions of people worldwide. The most common form of SC is NMSC which encompasses BCC and SCC. Although malignant melanoma is less common (4% of all dermatologic cancers), it accounts for 80% of all SC deaths. A review of the biology, epidemiology, clinical manifestations, and treatment options for SC sets the stage for an appraisal of the molecular mechanism of action AgNP technology as applied to SC management.

3.1 SC biology

Skin tissue, which is composed of epidermis, dermis, and connective tissue, serves a protective function in mammals. The dermis is composed of nerves, blood vessels, and lymphatic vasculature, embedded in a thick matrix of connective tissue [8]. Skin malignancy occurs when healthy skin cells deviate from their normal function and proliferate in an uncontrollable manner. MSC and
NMSC have different cells of origin and specific histology and clinical behavior [2] (Figure 1).

### 3.1.1 Melanoma

Melanoma, the deadliest form of SC, is initiated in melanocytes. Immunosuppression, sun sensitivity, and exposure to UV radiation in the setting of a genetic predisposition impact the genesis of melanoma [9]. Melanocytes, by function, are pigmented cells responsible for the production of skin and hair color. They are found in the basal layer of epidermis and in hair follicles [10]. Healthy melanocytes secrete melanin causing the tanning response, which absorbs UV radiation and prevents SC [11]. The absence of functional melanocytes in pigmentary disorders such as vitiligo and albinism results in greater susceptibility to the damaging effects of UV radiation [10]. Melanocytes also signal keratinocytes to secrete factors that enhance melanocyte survival, differentiation, proliferation, and motility. Mutations in key growth regulatory genes, secretion of autocrine growth factors, and the loss of adhesion receptors damage intracellular signaling in melanocytes [12]. Therefore, through BRAF (rapidly accelerated fibrosarcoma viral oncogene homolog B) mutation and activation of the mitogen-activated protein kinase (MAPK) pathway, melanocytes proliferate in a manageable fashion to form benign nevi (moles) [11]. Cytological observations of nevi reveal lesions within the cyclin-dependent kinase inhibitor 2A (CDKN2A) and phosphatase and tensin homologue pathways [9]. Further progression through decreased expression of microphthalmia-associated transcription factor leads to the radial-growth-phase MSC [10]. Modulation in expression of the melanocyte-specific gene melastatin 1 (TRPM1) advances the progression into vertical-growth phase cells which form nodules within the dermis which correlate with the metastatic potential of MSC [9]. Other events, including the loss of E-cadherin and increased expression of N-cadherin, αvβ3 integrin, and matrix metalloproteinase 2 (MMP-2), are common mutations in melanoma which reduce apoptosis prolonging the life of these rapidly proliferating melanocytes [9].

### 3.1.2 Basal cell carcinoma

BCC is capable of local tissue destruction and commonly recurs when incompletely excised. Fortunately, it rarely metastasizes. UV exposure from natural sources and tanning parlors is the most important modifiable risk factor in the development of BCC and explains the higher incidence of this tumor in men associated with outdoor occupations and older patients. Genetic conditions may also play a role [5]. Women may be catching up. Between 1973 and 2009, women below the age of 40 years presented a constant linear rise of 6.3% in BCC incidence rates associated with increased occupational and recreational UV light exposure [13]. BCC develops from germinative cells within the basal layer of the epidermis. Studies showed a differential expression of antigens by BCC, suggesting that tumor cells are proliferative and relatively undifferentiated. Chromosomal abnormalities observed in BCC are associated with invasiveness or histologic subtype of the tumor [14]. Mutations in components of the hedgehog (HH) signaling pathway lead to onset of BCC [15]. Both the autosomal dominant hereditary and non-hereditary forms of BCC are associated with the inactivation of tumor suppressor gene Patched 1 (PTCH1) stationed on chromosome 9q (see Figure 2) [16]. Seven-transmembrane domain G-protein coupled receptor-like protein Smoothened (Smo) is the zinc finger

![Figure 2: Interactions between Shh, Ptch-1, and Gli-1.](image-url)
protein (Gli) activator when Ptc is absent. Smo binds to
sonic hedgehog (Shh) while activating cytoplasmic Gli
transcription factors, thereby triggering an increase in
the expression of proteins required for cell proliferation
(Figure 2) [15].

3.1.3 Squamous cell carcinoma
SCC is the second most common form of SC with incidence
rates doubling in the past three decades [17]. Numerical
and structural chromosomal aberrations result from UV
exposure in epithelial keratinocytes and contribute to the
onset of SCC. Other risk factors include exposure to che-

micals, cigarette smoking, and human papilloma virus
[18]. UV-irradiated premalignant keratinocytes under-
gonal expansion, developing into actinic keratosis (AK)
[19]. Histological studies and molecular evidences have
proved that actinic keratoses are precursors of SCC [20].
Uncontrolled proliferation of these keratinocytes in the
epidermis produces SCC in situ, and dermal invasion is
the sine qua non of SCC. Photo-biological studies have
demonstrated that UV-R-related mutation accounts for
allelic loss on chromosomes, leading to complex genetic
alterations such as inactivation of tumor suppressor pro-
tein (p53), CDKN2A, amplification of rat sarcoma (RAS)
genes, and overexpression of RAS downstream proteins
like MAPKs and cyclins [21].

3.2 Epidemiology of SC
Skin is the largest organ of the human body, and predict-
ably the most common type of cancer is SC. The number
of SC cases has been increasing over the years, perhaps
attributing to a combination of factors including long-
vity, better SC detection, thinning of stratospheric ozone,
increased artificial UV exposure at tanning parlors, and
increased natural UV exposure at work and at play. The
most important modifiable risk factor for skin tumori-
genesis is UV radiation [22]. The effect of UV exposure is
cumulative in nature as the average age of diagnosis is
65 [7]. MSC is more prevalent in Caucasians than in other
ethnic groups (0.1% in Blacks and 0.6% in Hispanics) with
a lifetime risk of developing melanoma of about 2.6%. MSC
is more common among men; however, the rates are
higher in women before the age of 50 [7]. One rare form
of MSC, acral lentiginous melanoma, is more commonly
associated with dark skin and is not associated with UV
exposure [11].

Incidence rates for NMSC are about 18–20 times
higher than that of melanoma [23]. During the past 30
years, the worldwide incidence of SCC has been increasing
3–10% per year. During the same period, it is estimated
that the BCC incidence rate has risen between 20 and 80%
in the US [24]. A Swedish database of family cohort’s ana-
lysis revealed that intentional tanning is a contributing
factor in SCC incidence in the younger generation [25].
SCC has some association with geographic location as
higher incidence rates are observed in tropical regions
[26]. In addition, there is a correlation between SC and
immunity as patients who received organ transplantation
demonstrate a higher incidence of NMSC [27]. Limitations
in understanding the incidence of NMSC can be attributed
to geographic variability and inadequacy of data from
cancer registries.

3.3 Clinical manifestations of SC
Identification of SC is the most important step for physi-
cians, requiring a careful examination of the entire skin
surface. Clinically, skin tumors are diagnosed and prog-
nosis is assessed on the basis of their histopathological
appearance (Figure 3).

3.3.1 Melanoma
The diagnosis of primary superficial spreading malignant
melanoma is based on the clinical appearance of lesions. A
history of recent “change” in a pre-existing nevus or in the
appearance of a new pigmented lesion is most important in
the early diagnosis of melanoma [28,29]. These features are
highlighted in the ABCDE mnemonic for melanoma detec-
tion (Asymmetry, irregular Border, variegation of Color,
large Diameter greater than 4 mm, and Evolution of change
of pigmented lesion) [29]. There is an emphasis on the early
diagnosis of cutaneous malignant melanoma since the
depth of invasion in the skin and thickness of the lesions
are linked to disease prognosis. Malignant melanomas of
the skin are commonly found on the back, anterior torso,
upper extremities, head and neck in males, and the back,
lower legs, upper extremities, and head and neck in
females [30]. Melanoma can appear as a raised nodule
(nodular melanoma) or flat lesions on the palms of hands,
soles of feet, and in the nail bed (acral lentiginous mela-
nona) [31]. A number of other pigmented lesions can
resemble CM either clinically or histopathologically. These
include benign juvenile melanoma, blue nevus, halo
nevus, giant pigmented nevus, pigmented nevi on palms and soles, and melanotic freckle of Hutchinson [32].

3.3.2 Basal cell carcinoma

BCC lesions are classified clinically as nodular, superficial, and infiltrative based on their growth pattern and degree of differentiation [33]. Clinically, BCC appears as a small, pearly lesion on the face and other sun-exposed areas. As it grows, the tumor outstrips its blood supply and central ulceration and crusting occur. Thus, BCC often is described as the sore that will not heal. Superficial BCC appears as a scaling patch similar to nummular eczema, but these tumors do not itch (see Figure 3a). Larger plaque-like lesions demonstrate numerous pearly papulonodules with telangiectasias at the periphery of a crusted ulcer that has been described as rodent ulcer (see Figure 3b). Cystic nodules may also be present [33]. When BCCs are pigmented, they may mimic seborrheic keratosis or even malignant melanoma [34].

3.3.3 Squamous cell carcinoma

AK is the established precursor for SCC. It appears as 2–6 mm erythematous lesions with a sand-papery scale [19]. When this atypical proliferation of keratinocytes remains in the epidermis, the lesions are termed in situ. Bowen disease demonstrates sharply demarcated, erythematous, velvety, or scaly plaques on sun-exposed areas. The other common form of in situ SCC, erythroplasia of Queyrat, appears as a red, smooth plaque on the glans penis in uncircumcised men [19]. Invasive SCCs most commonly appear as expanding indurated, crusted, verrucous lesions plaques often with ulceration in sun exposed skin on the head and the neck [35,36] (see Figure 3c). Some SCC lesions are tender, but many are painless. SCC recurrence after treatment is associated with tumor size and factors such as degree of histological differentiation, depth of the lesion, perineural invasion, immune deficiency, and anatomic localization [5]. The lifetime risk of developing SCC in AK patients is 6–10% [37].

Figure 3: Clinical manifestations of different forms of skin cancer: (a) malignant melanoma distant view; (b) superficial BCC; (c) nodular BCC; (d) melanoma; (e) malignant melanoma with regression; (f) SCC (photographs were provided by Robert T. Brodell, MD, Professor and Chair, Department of Dermatology, University of Mississippi Medical Center, Jackson, Mississippi, USA).
3.4 Overview of current therapeutic strategies

The optimal treatment option for SC depends on the size, location, and developmental stage of the tumor. Common treatment for larger SCs includes excision, Mohs surgery, or radiation therapy, whereas smaller SCs may be treated with curettage and electrodessication, laser therapy, cryotherapy, or PDT [38].

3.4.1 Excisional surgery

Indolent primary tumors can be treated with elliptical excision. This method involves traditional histopathological processing and “bread-loafing” of the specimen every 1.5–2 mm. This provides a representative view of the tumor margin, but only 1% of the actual margin is viewed [39]. Advantages include histologic verification of tumor margins in representative sections, rapid healing, and the thin scar produced is cosmetically acceptable in the majority of patients. Disadvantages include the risks of hematoma, seroma, infection, and the potential for wound dehiscence [19].

3.4.2 Mohs surgery

Mohs micrographic surgery is a method of surgical excision in which the tumor is removed in stages in an outpatient setting using local anesthesia to ensure that the entire tumor is removed while sparing as much normal tissue as possible. The horizontal frozen sections produced in this manner provide visualization of 100% view of the peripheral and deep margins of each specimen [39]. It is cost-effective in comparison to traditional surgical excision methods [40]. Mohs micrographic surgery minimizes the potential for recurrence in patients with high-risk primary or recurrent BCC or SCC [41]. More recently, the Mohs technique has been used with immunohistochemistry stains to remove selected lesions of malignant melanoma in situ, especially those on the face near vital structures [42].

3.4.3 Curettage and electrodessication

Electrodessication and curettage is a technique involving the destruction of tumor and adjacent healthy tissue by cauterization, followed by scraping with a curette [37]. The process is repeated multiple times to increase the probability of complete removal of SC. Nonavailability of specimens for margin evaluation is a drawback [19]. Still, 5-year rates of cure in patients with small primary BCC and SCC are often above 90%. It is, however, not recommended for high-risk tumors [6].

3.4.4 Cryotherapy

Cryotherapy treatment uses liquid nitrogen to freeze primarily BCC and small SCC to tumoricidal temperatures [37]. This avoids complications of bleeding and most often heals in cosmetically acceptable fashion without the line scar typical of an excision. High rates of clearance have been reported [43]. The inability to determine margins and the operator-dependent nature of this process have resulted in this modality being uncommonly used for SC.

3.4.5 Radiation therapy

Radiation therapy is used in older patients with large, aggressive, or recurrent SC who cannot tolerate surgery or in locations where surgical removal is impossible [37]. It produces favorable functional and cosmetic results. It is often used in combination with other therapeutic modalities. High treatment costs, need for multiple visits, and the potential for recurrence of aggressive SC are disadvantages of radiotherapy [40].

3.4.6 Photodynamic therapy

Some superficial BCCs are treated with PDT. The systemic administration of hematoporphyrin derivative or dihematoporphyrin ether followed by irradiation from a tunable dye laser of 630 nm light has largely been supplanted by the topical application of aminolevulinic acid (ALA) followed by blue or red UV light [44]. The mode of action involves absorption of light by the active component — dihematoporphyrin ether generating singlet oxygen, which has cytotoxic effects [45]. Combination of PDT with other topical agents has been studied and found to be effective for superficial SCs [46].

3.4.7 Chemotherapy

Topical chemotherapy with 5-fluorouracil (5-FU), a structural analog of thymidine that hinders thymidylate
inducing apoptosis activity of the drug temozolomide against melanoma approved drugs that inhibit the HH signaling pathway. Itraconazole, sonidegib, and vismodegib are FDA therapies for BCCs. HH signaling pathway, regulated by FGFR1/2, is increased in correlation with the aggressiveness of skin tumors [52].

Studies with non-steroidal anti-inflammatory drugs (NSAID), such as oral and topical celecoxib and topical diclofenac, have demonstrated chemopreventive effects by inhibiting angiogenesis and stimulating apoptosis, primarily via cyclooxygenase-2 (COX-2) inhibition [51]. It was shown that levels of COX-2 increased in correlation with the aggressiveness of skin tumors [52].

3.4.8 Targeted immunotherapy

High-dose interleukin (IL)-2, interferon (INF)-α, dacarbazine, carmustine, paclitaxel (taxol), temozolomide, and cisplatin are the most widely used adjuvant immunotherapies for advanced melanoma [9]. Immunotherapy with ipilimumab and the MAPK-targeted inhibitors vemurafenib, dabrafenib, and trametinib are targeted treatment options available for SC patients [11]. Ipilimumab is a Food and Drug Administration (FDA) approved drug for adult patients with metastatic melanoma that acts as an antibody against cytotoxic T-lymphocyte antigen-4 (CTLA-4). It blocks CTLA-4, thereby allowing appropriate T lymphocytes activation. These events restore T-cell proliferation while enhancing the patient’s capacity to survive because of the antitumor immune response [53]. Similarly, the proteasome inhibitor PS-341 has been shown to enhance activity of the drug temozolomide against melanoma [54]. Smoothened (SMO) inhibitors are highly targeted therapies for BCCs. HH signaling pathway, regulated by activating mutations in SMO, is critical in BCC pathogenesis. Itraconazole, sonidegib, and vismodegib are FDA approved drugs that inhibit the HH signaling pathway [55–57]. Chemotherapeutics, such as INF-α and 13-cis-retinoic acid, have been used primarily for SCC in the past [58]. Cemiplumab was recently approved by FDA for the treatment of severe and metastatic SCC [59].

Intralesional injection of IFN has shown promising results in the treatment of NMSC by modulating the development and function of humoral or cell-mediated responses to antigens [60]. Combination therapy of BCC with alfa 2a and 2b has shown to be synergistic through cluster of differentiation 95 (CD95) ligand–CD95 receptor interaction.

Imiquimod is another promising topical therapy in the management of select NMSC cases. It promotes immune stimulation by binding to cell surface receptors (toll receptor 7) and stimulating the secretion of cytokines (IL-1, tumor necrosis factor α (TNFα), IL-6, IL-10, and IL-12) producing antitumor effects through mitochondrial mediated apoptosis [61]. The list of some chemical compounds used as biopathway inhibitors for SC treatment is shown in Table 1. The mechanism of action is unknown for some forms of INF treatment as topical immunotherapy. Side effects of flu-like symptoms with one instance of sero-positive rheumatoid arthritis have been reported [62].

Recent studies have proven that epidermal growth factor receptor (EGFR) inhibitors are frequently responsible for cutaneous drug reactions causing an adverse effect on life expectancy, and hence leading to the discontinuation of treatment [63]. It has also been reported that the therapy for larger BCC lesions was less effective as the focus on treating superficial portions of the tumor left a deeper component undetected [64].

3.4.9 Herbal supplements

There is a potential role for dietary and herbal supplements in the prevention and treatment of cutaneous
3.5 Biomedical applications of nanotechnology in SC treatment

Systemic treatments for skin problems produce potential adverse effects that impact health. Better drug delivery systems that efficiently deliver therapeutic agents through the skin barrier are needed. Optimally, this would be done without chemical enhancers that may damage epidermal cell cohesion and stratum corneum lipids.

Nanotechnology is a blooming area for skin health maintenance, as well as for the diagnosis and management of cutaneous disease. Nanotechnology relies on the interaction at the sub-atomic level with the skin tissue [67]. Drug permeation/penetration is modified via controlled release of active substances by increasing the period of stability on the skin [68], establishing direct contact with the stratum corneum and skin appendages [69], and protecting the drug against chemical or physical instability.

In addition, NPs provide high efficacy, specificity, and cost-effective treatment options [67]. Evidence from research developments in the fields of drug delivery through enhanced skin penetration by NPs is very promising [70]. This is the result of improved methods such as differential stripping, spectrophotometry, and confocal laser scanning microscopy that improve our understanding of intrafollicular drug delivery and kinetics for a variety of drugs across the skin barrier [70].

Nanotechnology research focused on dermatology is ongoing in the development of consumer products (screens, fillers, antimicrobials, and wound care), devices for real-time diagnosis and visualization of tumors, diagnostics for sentinel lymph node assessment, and therapeutic agents including antimicrobials, epidermally localized corticosteroids, gene silencers, epidermaceous vaccines, and inducible therapies activated by optical, magnetic, temperature, and radiofrequency [71].

3.5.1 Drug delivery

The transdermal approach for drug delivery offers the potential for precise targeting of SC [72]. The major challenge is to increase skin permeation of the antineoplastic drug to permit an adequate pharmacological dose. Anticancer drugs that possess hydrophilic properties have a low oil/water partition coefficient, high molecular weights, and ionic characters that impede penetration through the stratum corneum barrier [73]. According to Fick’s second law, the bioactivity of a drug is dependent upon drug permeation, drug concentration in the vehicle, the partition coefficient between the formulation and the stratum corneum, the membrane thickness, and the diffusion coefficient of the drug in the stratum corneum [74]. Nanocarriers such as liposomes, dendrimers, polymersomes, carbon-based NPs, inorganic NPs, and protein-based NPs increase drug concentration in the vehicle and, thereby, increase drug flux [75]. In the following section, several nanocarriers will be discussed with an emphasis on activity against skin neoplasms.

3.5.2 Magnetic NPs

Magnetic NPs are useful tools for theragnostics (the fusion of therapeutic and diagnostic technologies) [76]. Albumin loaded magnetic nanocomposite spheres with 5-FU has been used to treat NMSC [77]. This improves the penetration of 5-FU and also minimizes the side effects of conventional topical drugs. In addition, in vitro studies on magnetic nanoemulsion loaded with zinc phthalo cyanine showed great potential as synergic application for SC treatment [78]. Cetuximab-coated thermosensitive liposomes loaded with magnetic NPs and doxorubicin have been tested for its efficacy in breast cancer cell-targeted EGFR NP-liposome drug delivery system [79].

3.5.3 Liposomes

Liposomes are one of the most studied nanocarriers for the treatment of cancer [75]. They are spherical shaped, small artificial vesicles synthesized from cholesterol and natural non-toxic phospholipids. Liposomes are promising systems for drug delivery because of their size and hydrophobic and hydrophilic character [80]. Liposomes loaded with doxorubicin [81,82], cisplatin [83,84], oxaliplatin [85], and camptothecin [86] have been used systemically to enhance drugs’ cytotoxicity with minimum side effects. Combinations of topical drugs such as tretinoin and diclofenac-loaded liposomes have demonstrated improvement in skin penetration of the drug, over nonliposomal formulations [87,88]. A randomized study of the effect of topical application of liposome encapsulation of T4 endonuclease V lotion in xeroderma pigmentosum represents a new
drug delivery approach that transports enzymes through human stratum corneum and presents biologically active proteins into viable epidermis [89]. Thermosensitive betulinic acid-loaded magnetoliposomes showed antitumor activity against aggressive human breast adenocarcinoma cells under hyperthermic conditions [90].

3.5.4 Solid lipid NPs

The NPs, which have been most studied for delivery of topical medications, are solid-lipid NPs and polymeric NPs, synthesized from poly (dl-lactic acid), poly (lactic-co-glycolic acid) (PLGA), and poly-ε-caprolactone [91]. Topical application of both solid-lipid NPs and polymeric NPs promotes constant drug release and protection against drug degradation, thereby achieving targeted drug delivery [75]. Application of drugs (doxorubicin) [92], natural compounds (sesamol and resveratrol) [93,94], and photosensitizer (PS) (aluminum chloride phthalocyanine) [95] loaded with solid lipid NPs demonstrates potential for the development of effective SC treatments.

3.5.5 Photodynamic therapy

Topical PDT induces a cytotoxic effect by activation of a PS prodrug, ALA or its methylated ester (methyl aminolevulinate [MAL]), converted by the heme biosynthetic pathway mostly to protoporphyrin IX. Treatment is accomplished by irradiation with a specific UV wavelength in the absorbance spectrum of the drug in the presence of oxygen [75]. This non-surgical treatment method, approved by the FDA, has potential to clear actinic keratoses and superficial BCC and prevent new lesions from occurring. Treatment of a cancerization field enhances the Raman scattering of abnormal growth across weak signal from normal tissue [104].

3.6 Diagnosis

NPs are excited by a white light from a halogen lamp, while a dark field condenser delivers and focuses it on the top of the sample, providing an image of bright object in a dark background with brilliant color depending on the size and shape of the particles. Conjugation of NPs with antibodies by nonspecific adsorption strongly scatters signals facilitating the detection of abnormal growth across weak signal from normal tissue [104].

Gold nanorod might also be used as imaging contrast agents for cancer diagnosis with a conventional optical microscope. Because of high scattering cross-sections and superior photostability of gold (Au) NPs, anti-EGFR-conjugated Au NPs bind specifically to the cancer cells, because of their overexpression on the cytoplasmic membrane of the malignant cells [105,106].

Magnetic NPs enhance targeting with specific cell labeling for early diagnosis of SC [107]. Recent studies revealed a simple and rapid colorimetric detection of melanoma circulating tumor cells using bifunctional magnetic NPs [108]. AgNP-embedded nanoshell structure is used in cancer imaging and photothermal therapy to absorb light and destroy them via photothermal effect [109].

In addition, the field enhances the Raman scattering of adjacent molecules causing a phenomenon called surface-enhanced Raman scattering (SERS) [110]. Because of Raman intensity directly proportional to the square of the
field intensity imposed on the molecules, near-infrared-sensitive SERS nanoprobes used for molecular imaging of target cancer cells successfully demonstrated targeting, isolation, and imaging of cancer cells [111]. Through M-SERS conjugated targeting antibodies, the specific cancer cells could easily be isolated by an external magnetic field in a multiple cell population. Application of SERS by gold nanorods to diagnose cancer cells from normal cells specifically bound to human oral cancer cells [112]. Raman tagging is another novel approach where an organic dye molecules with aromatic structures attached to the NPs by physically adsorption or chemically conjugation [113–116]. In addition, multiplexing with SERS labels of Raman reporter molecules is also possible [117].

In light of this, NP-mediated diagnosis appears to be a promising approach for an effective SC treatment by significantly improving detection sensitivity while reducing the signal acquisition time, thereby creating new developments of SERS from bench top to in vivo applications and opportunities for further clinical imaging system centered on Raman spectroscopic cancer detection.

### 3.7 AgNP in nanotherapy

AgNPs are the most widely used NPs among all other NPs because of their antibacterial properties [118]. They are high-demand materials for consumer products because of their unique physical and chemical properties. Studies on potential therapeutic implications of AgNPs reveal their wide applications in medicine. AgNPs have been used in medicine, medicinal devices, pharmacology, biotechnology, electronics, engineering, energy, magnetic fields, and also in environmental remediation [119]. Recently, AgNPs have been widely used in healthcare products, the food industry, paints, cosmetics, female hygiene products, medical devices, sunscreen, biosensors, clothing, and electronics [120].

### 3.7.1 Antibacterial activity of AgNPs

AgNPs are capable of attacking wide variety of pathogens at low concentrations [121]. The multiple antibacterial mechanisms of AgNPs lower the risk of antibiotic resistance. Molecular mechanism of bacterial cytotoxicity involves destruction of cell wall, production of ROS, and damage of DNA [122].

### 3.7.2 Anticancer effect of AgNPs

Experimental studies have been conducted on the cytotoxicity of AgNPs in different cancers including cervical cancer, breast cancer, lung cancer, hepatocellular carcinoma, nasopharyngeal carcinoma, hepatocellular carcinoma, glioblastoma, colorectal adenocarcinoma, and prostate carcinoma [123]. Contributing factors for effective treatment include dose, time of exposure, and size and shape of the AgNP. Molecular mechanisms of AgNP-mediated apoptosis involve production of ROS, mitochondrial membrane disruption, DNA damage, and signaling pathways leading to programmed cell death [124].

### 3.7.3 Other medical applications

AgNPs exhibit special physicochemical properties resulting in their wide-spectrum of application in medicine. AgNPs can increase the wound healing rate probably by inducing angiogenesis. Advantages over conventional treatment methods include shorter period and a superior cosmetic appearance, including nearly normal hair growth and less hypertrophic scarring [125]. AgNPs can be used as doping materials for synthetic bone supports [126]. They also play a role in fracture healing as an osteoconductive biomaterial by stimulating proliferation and osteogenic differentiation of mesenchymal stem cells [127]. AgNPs conjugated with polymethyl methacrylate have been used to treat dental dentures through their antibacterial activity since AgNPs reduce biofilm formation [128]. AgNPs have also been reported to enhance the immunogenicity of vaccines by loading with suitable concentrations of NPs [129]. AgNPs also exhibit anti-diabetic effect via influencing insulin signaling pathway [130].

### 3.7.4 Biosensing and bioimaging

AgNPs have been extensively applied in various subfields of nanomedicine such as nanoelectronics, diagnostics, molecular imaging, and biomedicine by their enhanced electromagnetic fields [131]. In the following sections, we discussed few applications of nanotechnology in diagnosis of a disease.

#### 3.7.4.1 Plasmonic nanoantennas

AgNPs act as highly sensitive probes beneficial for targeting and imaging of small molecules, DNA, proteins,
cells, tissues, and even tumors in vivo [109,132,133]. AgNPs behave as nanoscale antennas by enhancing the electromagnetic intensity in its vicinity. SERS technique makes use of the enhanced electromagnetic field, where molecules can be recognized based on their distinctive vibrational modes. SERS helps in the early detection of cancer biomarkers or the detection of drug levels in the blood and other body fluids. M-SERS, along with targeting antibodies, has an ability to specifically target and sort the cancer cells and isolate them by an external magnetic field [131]. This method works by adsorption of molecules on AgNPs where strong field enhancement is generated in the nanogaps for detection to the factor of $10^8$–$10^{12}$ [134]. In a previous study, silica-encapsulated silver-embedded magnetic AgNPs produced stronger SERS signals for targeting breast cancer cells and floating leukemia cells [135]. Using this method, targeted cells can be easily separated from multiple cell population.

### 3.7.4.2 Nanobiosensor

AgNPs can absorb and scatter light with powerful efficiency. Nanobiosensor is an innovative combination of nanotechnology and optical biosensor finding its application in medical, food safety, environmental monitoring, and drug screening [116,136]. The localized surface plasmon resonance (LSPR)-based nanobiosensor is a new type of optical biosensor technique developed by excitation when the incident photon frequency is resonant with the collective oscillation of the conduction electrons. Recently, LSPR biosensor based on AgNPs for the detection of p53 protein levels from HNSCC patients has been designed [137]. In addition, a combination of triangular plate-shaped AgNPs of different sizes with monoclonal antibodies (mAb) that bind to specific biomarkers acts as a multiplexed lateral flow point-of-care (POC) sensor [138]. AgNPs have become an answer for efforts to develop a POC detection for chronic and acute sickness.

### 3.7.4.3 Metal-enhanced fluorescence

Metal-enhanced fluorescence is a biotechnology-based tool where metallic nanostructures are used to alter the spectral properties of fluorophores for improved detection in immunoassays, ratiometric sensing, and DNA detection. Regulation in radiative decay rates and resonance energy transfer seems to be the primary role of metal NPs to increase detection sensitivity. Thiolated oligonucleotides conjugated to AgNPs on a glass substrate resulted in substantial increase in fluorescence intensity [139]. Enhanced ratiometric fluorescence detection has become possible through silver island films providing up to tenfold increases in fluorescence signal [140]. In addition, metal-enhanced solution assays, fluorescent probes, and planar immunoasays have been proved to show the usefulness of AgNP-enhanced fluorescence [141].

### 3.7.5 AgNP and SC

With regard to AgNP and SC, their absorption through intact and damaged skin was very low but detectable. However, in case of damaged skin, increased permeation has been observed [142]. In contrast, another study has revealed that AgNPs were able to penetrate through the intact human skin in vivo and could be found beyond the stratum corneum at depths of the reticular dermis [143]. The penetration of AgNPs is linked to the size of AgNPs. Human epidermal keratinocytes’ cytoplasmic vacuoles showed the presence of AgNPs (20, 50, and 80 nm) [144], while 100 nm diameter AgNPs were unable to penetrate into the human epithelial line [145] and 0.002–0.02 ppm AgNPs did not penetrate through intact human epidermal keratinocyte cell line (HaCaT) keratinocytes [146].

Dermal and systemic absorption of AgNPs through healthy human skin seems to have different approach. After penetration from intact human skin in vivo beyond the stratum corneum, absorbed silver appears as clusters in silver oxide form across the epidermis [143].

It has recently been suggested that AgNPs may increase the rate of wound closure through the initiation of proliferation and migration of keratinocytes and could trigger the differentiation of fibroblasts into myofibroblasts, thereby promoting wound contraction [147]. The effect of AgNPs on the functionality of repaired skin is through regulation of skin collagen deposition leading to improved tensile properties and better fibril alignments in repaired skin [148]. However, the AgNP-modulated signaling pathway for collagen regeneration is yet to be explored.

AgNPs pretreatment significantly reduced the extent of apoptosis caused by UVB radiation in HaCaT cells as well as induces G1/S phase cell-cycle arrest. Higher internalization of AgNPs in UVB-irradiated cells indicates the involvement of nucleotide excision repair genes in the repair of UVB-induced DNA damage [22].
AgNPs are synthesized by wide range of processes such as physio-chemical, physical, and chemical techniques via appropriate choice of energy source, precursor chemicals, reducing and capping agent, as well as through concentration and molar ratio of chemicals [131]. However, the photochemical synthesis method produces shape and size-controlled AgNPs for conjugating biomolecules such as DNA probes, peptides, and antibodies, which can be beneficial for targeted chemotherapy. This method involves physisorption of the biomolecule on the surface of Ag while irradiating Ag seed solution with a light of selected wavelength [131].

### 3.7.6 Properties of AgNPs

The physicochemical properties of AgNPs include shape, surface charge and coating, agglomeration, dissolution rate, and LSPR [149]. Previous studies concluded that the electromagnetic, optical, and catalytic properties of AgNPs can be strongly influenced by their size, shape, and distribution, which can often be varied by altering the synthetic methods, reducing agents, and stabilizers [150]. The extent of AgNP cytotoxicity is determined by their surface charge and size. Smaller particles induce greater toxicity because of their larger surface area [151]. Commonly used silver nanostructures in the biomedical field are spherical AgNPs, nanowires, nanorods, nanoplates, and nanocubes [152]. Different surface charges of AgNP coatings regulate the NP interaction with various biomolecules at the target site [153]. Nano-sized drug formulations regulate skin penetration of the drug depending on design and physicochemical properties of the ingredient [154]. Several studies have focused on the physical and chemical properties of cubosomes in designing anticancer drugs [155]. Therapeutic use of nanodiamonds has been motivated by their potentially advantageous properties such as inertness, small size, and surface structure for labeling and drug delivery [156].

### 3.7.7 Mechanisms of toxicity of AgNP to cancer cells

In spite of a significant research effort focused on the applications of AgNPs, very few studies have been examined on the mechanism of AgNP cytotoxicity. Cytotoxicity depends not only on the NP’s properties but also on the specific organism [157]. The cytotoxic and genotoxic effects of AgNPs depend on the duration, dosage, and temperature along with size, surface coatings, and cell types [158]. The uptake of AgNPs is mainly through endocytosis via lysosomes [159]. Exposure to the acidic environment of lysosomes leads to dissolution of AgNPs into Ag ions producing hydroxyl radicals [158]. The internalized AgNPs disrupt the integrity of the cell membrane, causing lysosomal swelling and even rupture lysosomal membranes [160]. The released Ag ions interact with reduced glutathione S-transferase, superoxide dismutase in the cytoplasm, cell membrane, and inner membranes of a mitochondrion affecting membrane integrity. Furthermore, damage to mitochondria impairs electron transfer, inhibits adenosine triphosphate synthesis, and triggers oxidative stress through lipid peroxidation [161]. AgNPs induce apoptosis through mitochondrial, intrinsic, or p53-mediated pathway [162]. All these events inhibit cell proliferation through cell-cycle arrest in the G2/M phase [163]. Downregulation of total protein kinase B (AKT) and high expression of p38 are documented along with increased expression of H2A histone family member X (H2AX), Caspase-3, p-p53, and total p53 [164]. AgNP-induced phosphorylation of histone protein leads to activation of c-Jun N-terminal kinase (JNK) pathway [165]. Images from transmission electron microscopy and elemental mapping of single cells have revealed that AgNPs can translocate to the nucleus and cause DNA damage inducing mutations [158] In addition, AgNP can activate a range of pathways such as MAPK and nuclear factor kappa-light-chain-enhancer of activated B (NFκB) pathways resulting in transcription of many genes involved in the proliferation and inflammatory response [166]. Differential regulation of intracellular factors mediating cell cycle, DNA repair, and inflammation have been associated with AgNP-induced cytotoxicity [167]. A schematic representation of AgNP-induced cytotoxicity is explained in Figure 4 for better understanding of the mechanism.

### 4 Strategies to overcome toxicity

Recognizing that early detection of SC leads to successful treatment with conventional surgical procedures, large tumors, metastatic foci, and tumors near vital structures are best treated with evolving medical therapies, including drug-based chemotherapy, cell-based therapies, and immunotherapy [168,169]. To minimize the side effects of systemic administration of the anticancer pharmaceuticals (e.g., intravenous injections or oral), topical formulations and transdermal alternatives provide novel strategies of drug delivery systems for the effective chemotherapy SC [170].

Although AgNPs induce acute toxic effects to various cultured cells, the toxic effects to normal cells are
unclear. The toxicity of AgNPs depends on the particle size, shape, and their surface properties [171–173]. Adverse side-effects can be minimized with polymer–drug conjugates while enhancing drug efficiency, by active or passive targeting of the specific diseased-tissue site [174]. In this section, we briefly discuss the strategies to overcome AgNP toxicity.

### 4.1 Nanocarriers

With the advent of polymer therapeutics, improved solubility of the drug, enhanced bioavailability associated with higher biochemical stability, controlled drug release targeted to specific tissues and organs, and the potential reduction of the total dosage of the drug have been accomplished [13]. Angiogenic niche is the potential site for targeting the nanocarrier [175]. The successful delivery depends on cellular structure of tumor cells, endothelial cells, and disfigured cell shape, along with cell integrity, overcoming immediate clearance from systemic circulation because of engulfing with macrophages and spleen [176,177]. Therefore, physicochemical characterization (particle size, surface charge, density, surface topography) and physiological condition of target site are important for the delivery of nanocarrier [178]. The amount of drug permeated and deposited in skin layers can be altered by adding different kind of nanocarriers such as ethosomes and liposomes to surmount the skin barrier structure and to deliver drugs for the inhibition of UV-induced DNA damage and skin carcinogenesis [179,180]. Therefore, the development of embedded nanomaterials such as liposomes, polymer micelles, silicon dioxide, carbon nanotubes, dendritic polymers, gold, silver, and other metal or metal oxides, associated or not with drugs, has been a burgeoning field in recent years [181–183]. Not only AgNP, cerium oxide, and zinc oxide have been extensively studied for melanoma treatment as a recent development in nanomedicine [184]. Surface coating of AgNPs can affect shape, aggregation, and dissolution rate [99]. The type of coating depends on the capping agent properties providing additional functionality [157]. Capping agents seem to enhance the thermodynamic stabilization of NPs by increasing the electrostatic, steric, or electrosteric repulsive forces between NPs, thus preventing their aggregation [185]. Two primary categories of capping agents are organic capping agents (polysaccharides, citrates, polymers, proteins, etc.) and inorganic capping agents (sulfide, chloride, borate, and carbonate) [157]. Polyethylene glycol (PEG)-coated NPs demonstrated stability in highly concentrated salt solutions, whereas lipoic acid-coated particles with carboxyl groups can be used for bioconjugation [131]. Novel study on multidrug resistant tumor cells treated with nanosilver modified with transactivating transcriptional activator (TAT) cell-penetrating peptide showed 24-fold higher toxicity. Same study similarly showed significantly reduced adverse toxicity in a mouse melanoma model [186]. Polystyrene-coated AgNP caused few genetic changes compared to uncoated NPs based on cell viability assay, micronucleus test, and DNA microarray analysis [187]. Thymoquinone PLGA (TQ–PLGA) NPs formulated and characterized using an active compound extracted from *Nigella sativa* – TQ is a biocompatible coating material (TQ–PLGA NPs) with the evaluation of its therapeutic properties in human melanoma cancer cells with 96.8% encapsulation efficiency [188]. Other evidence demonstrates that

---

**Figure 4:** Signaling pathway of AgNP-induced apoptosis.
AgNP coatings interfere with normal healthy skin cells. In a comparative study to understand the behavioral, developmental, and morphological changes on fish treated with AgNPs of different sizes and coatings, it was found that capped AgNPs are less potent than Ag⁺. Therefore, toxicological effects highly depend on particle coating and size, rather than the release of Ag⁺ alone [189]. In addition, citrate, a widely used reducing and capping agent, and PVP-coated AgNPs were tested to be less cytotoxic against human colorectal adenocarcinoma cells [190]. It is noted that surface coating of NP can significantly affect the AgNP-induced cytotoxicity. Alginate and Poly 4-styrenesulfonic acid-co-maleic acid (PSSMA) capping agents are selectively toxic to the cancer cell line but not to the normal cell line. These results confirm that one of the determining factors for toxicity of AgNPs is the type of capping agent [191]. Nevertheless, the question still remains whether AgNPs can affect keratinocytes and fibroblasts during the healing process.

### 4.2 Green synthesis

Because of the toxic side effects of AgNPs to non-target organs, green synthesis of AgNP has been proposed as a promising technique for SC management. Similar to other synthesis methods, physical characteristics such as size and shape of the NPs are altered by controlling pH and temperature [192]. Green synthesis of AgNPs involves the utilization of bacteria, fungi, yeasts, algae, or plant extracts as reducing and/or stabilizing compounds [157]. Previous studies compared toxicity levels of these green synthesized AgNPs to chemically synthesized synthetic AgNPs [193]. Biosynthesis of AgNPs from different plant parts exhibited cytotoxic effect on skin cells in a dose-response way (Table 2). Several kinds of biosynthesized AgNPs, using bacteria and natural products, have been used in SC. This method of producing ecologically safe AgNPs reduces the toxic by-products and usage of hazardous chemicals. The benefits of NP biosynthesis include simpler processing methods, shorter synthesis times, high yield, low toxicity, and biocompatibility [194]. Several studies have tested the anticancer effect of green AgNPs on SC. Spherical AgNPs prepared through one-step reaction from *Carpesium cernuum* whole plant extract from reduced silver ions were cytotoxic on *Mus musculus* skin melanoma cells [195]. Dose-dependent antioxidant activity has been observed in skin melanoma cells. A recent study demonstrated that the conjugation between curcumin and silver in nanoform (AgNP-PEG) improved the photostability of curcumin, inducing cytotoxicity on different skin cell lines [196]. Seed extracts of *Trigonella foenum-graecum* have anticancer efficacy against A-431 [197]. Biosynthesized AgNPs of different shapes from *Cucurbita maxima* (petals), *Moringa oleifera* (leaves), and *Acorus calamus* (rhizome) extracts showed anticancer activity against skin carcinoma [198].

### Table 2: Green synthesized silver nanoparticles

| Plant species     | Compound                   | References |
|-------------------|----------------------------|------------|
| *Euphorbia peplus*| Ingenol mebutate           | [208]      |
| *Hypericum perforatum*| Hypericin                  | [209]      |
| *Coffea arabica* | Coffea                     | [210]      |
| *Camellia sinensis*| Tea                       | [211]      |
| *Cucumis longa Linn.* | Curcumin                 | [212]      |
| *Glycine max* | Genistein                  | [213]      |
| *Vitis vinifera* | Proanthocyanidin           | [214]      |
| *Solanum lycopersicum*| Lycopene                 | [215]      |

### 5 Conclusions

SC is a prevalent cancer in human populations and is the cause of significant morbidity and mortality. The treatment of both MSC and NMSC includes excisional surgery, Mohs micrographic surgery, curettage and electrodessication, cryotherapy, radiation therapy, PDT, immunotherapy, and chemotherapy, depending on the cancer type, site of occurrence, and patient characteristics. Although standard topical chemotherapy drugs (imiquimod, 5-FU, retinoid, NSAID) and systemic immunotherapy with biopathway inhibitors (vemurafenib, binimetinib, nivolumab, cemiplimab, sonidegib, etc.) have been used widely, the potential side effects of these drugs have led to the development of new therapeutic agents. One approach is the application of nanotechnology in biomedicine, most importantly the evaluation of engineered AgNPs in the diagnosis and management of SC. Research has demonstrated that AgNPs are cytotoxic to SC cells, and their toxicity is mediated through a biochemical mechanism that is triggered by oxidative stress leading to genotoxicity, p53 activation, and apoptosis. The concern over the potential toxicity of AgNPs to normal skin cells led to green synthesis approaches that have been used to produce and test more suitable drugs. The toxicity of these agents is highly dependent upon particle size, shape, and surface properties. There is scientific evidence indicating that the toxicity of NPs to non-target cells can be significantly reduced by modifying their physicochemical properties.
Acknowledgments: This research was funded by NIH/NIMHD grant #G12MD007581 (RCMI-Center for Environmental Health), NIH/NIMHD grant #1US4MD015929 (RCMI Center for Health Disparities Research), and NSF grant #HRD 1547754 (CREST Center for Nanotoxicity Studies) at Jackson State University, Jackson, Mississippi, USA.

Conflict of interests: The authors declare no conflict of interest regarding the publication of this paper.

References

[1] Jou PC, Tomecki KJ. Sunscreens in the United States: current status and future outlook. Adv Exp Med Biol. 2016;26:464–84.
[2] Narayanan DL, Saladi RN, Fox JL. Ultraviolet radiation and skin cancer. Int J Dermatol. 2010;49:978–86. doi: 10.1111/j.1365-4632.2010.04474.x.
[3] Marks R. Epidemiology of melanoma. Clin Exp Dermatol. 2000;25:459–63. doi: 10.1046/j.1365-2230.2000.00693.x.
[4] Leiter U, Eigentler T, Garbe C. Epidemiology of skin cancer. Adv Exp Med Biol. 2014;44–55. doi: 10.1016/b978-1-4377-1788-4.00005-8.
[5] Apalla Z, Nashan D, Weller RB, Castellsagué X. Skin cancer: epidemiology, disease burden, pathophysiology, diagnosis, and therapeutic approaches. Dermatol Ther (Heidelberg). 2017;7:5–19. doi: 10.1007/s11555-016-0165-y.
[6] Wehner MR, Shive ML, Chen MM, Han J, Qureshi AA, Linos E. Indoor tanning and non-melanoma skin cancer: systematic review and meta-analysis. BMJ. 2012;345:e5909. doi: 10.1136/bmj.e5909.
[7] Institute NNC. Cancer facts & figures 2020. CA Cancer J Clin. 2020. https://www.cancer.org/content/dam/cancer.org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf.
[8] Kanitakis J. Anatomy, histology and immunohistochemistry of normal human skin. Eur J Dermatol. 2002;12(4):390–401.
[9] Miller AJ, Mihm MC. Melanoma. N Engl J Med. 2006;355:51–65. doi: 10.1056/NEJMra052166.
[10] Siominski A, Tobin DJ, Shibahara S, Wortsman J. Melanin pigmentation in mammalian skin and its hormonal regulation. Physiol Rev. 2004;84:1355–228. doi: 10.1152/physrev.00044.2003.
[11] Gray-Schopfer V, Wellbrock C, Marais R. Melanoma biology and new targeted therapy. Nature. 2007;445:851–7. doi: 10.1038/nature05661.
[12] Haass NK, Smalley KSM, Herlyn M. The role of altered cell-cell communication in melanoma progression. J Mol Histol. 2004;35:309–18. doi: 10.1023/B:HIJO.0000032362.35354.bb.
[13] Flohil SC, Seubring I, Van Rossum MM, Coebergh JWW, De Vries E, Nijsten T. Trends in basal cell carcinoma incidence rates: a 37-year Dutch observational study. J Invest Dermatol. 2013;133:913–8. doi: 10.1038/jid.2012.431.
[14] Miller SJ. Biology of basal cell carcinoma (part I). J Am Acad Dermatol. 1991;24:1–13. doi: 10.1016/0190-9622(91)70001-1.
[15] Celebi ARC, Kiratli H, Soylemeyozoglu F. Evaluation of the ‘Hedgehog’ signaling pathways in squamous and basal cell carcinomas of the eyelids and conjunctiva. Oncol Lett. 2016;12:467–72. doi: 10.3892/ol.2016.4625.
[16] Indri I, Gottschling M, Stockfleth E. Human papillomaviruses and non-melanoma skin cancer: basic virology and clinical manifestations. Dis Markers. 2007;23:247–59. doi: 10.1155/2007/942650.
[17] Rogers HW, Weinstock MA, Harris AR, Hinckley MR, Feldman SR, Fleischer AB, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. Arch Dermatol. 2010;146:283–7. doi: 10.1001/archdermatol.2010.19.
[18] Herzberg AJ, Kerns BJ, Honkanen PA, Pence JC, Iglehart JD, Kinney RB. DNA ploidy and proliferation index of soft tissue sarcomas determined by image cytometry of fresh frozen tissue. Am J Clin Pathol. 1992;97:529–37.
[19] Alam M, Ratner D. Cutaneous squamous-cell carcinoma. N Engl J Med. 2001;344:975–83. doi: 10.1056/NEJM200103293441306.
[20] Rehman I, Takata M, Wu YY, Rees JL. Genetic change in actinic keratoses. Oncogene. 1996;12:2483.
[21] Boukamp P. Non-melanoma skin cancer: what drives tumor development and progression? Carcinogenesis. 2005;26:1657–67. doi: 10.1093/carcin/bgi123.
[22] Arora S, Tyagi N, Bhardwaj A, Rusu L, Palanki R, Vig K, et al. Silver nanoparticles protect human keratinocytes against UVB radiation-induced DNA damage and apoptosis: potential for prevention of skin carcinogenesis. Nanomed Nanotechnol Biol Med. 2015;11:1265–75. doi: 10.1016/j.nano.2015.02.024.
[23] Eide MJ, Krajenta R, Johnson D, Long JJ, Jacobsen G, Asgari MM, et al. Identification of patients with nonmelanoma skin cancer using health maintenance organization claims data. Am J Epidemiol. 2010;171:123–8. doi: 10.1093/aje/kwp352.
[24] Wadhera A, Fazio M, Bricca G, Stanton O. Metastatic basal cell carcinoma: a case report and literature review. How accurate is our incidence data? Dermatol Online J. 2006;12:4.
[25] Hemminki K, Zhang H, Czene K. Time trends and familial risks in squamous cell carcinoma of the skin. Arch Dermatol. 2003;168:501–7. doi: 10.1001/archderm.139.7.885.
[26] Qureshi AA, Laden F, Colditz GA, Hunter DJ. Geographic variation and risk of skin cancer in US women: differences between melanoma, squamous cell carcinoma, and basal cell carcinoma. Arch Intern Med. 2008;168:501. doi: 10.1001/archinte.168.5.501.
[27] Moloney FJ, Comber H, O’Lorcan P, O’Kelly P, Conlon PJ, Murphy GM. A population-based study of skin cancer incidence and prevalence in renal transplant recipients. Br J Dermatol. 2006;154:498–504. doi: 10.1111/j.1365-2133.2005.07021.x.
[28] Rigel DS, Friedman RJ, Kopf AW, Polsky D. ABCDE – an evolving concept in the early detection of melanoma. Arch Dermatol. 2005;141:1032–4. doi: 10.1001/archderm.141.8.1032.
[29] Zaharna M, Brodell RT. It’s time for a “change” in our approach to early detection of malignant melanoma. Clin Dermatol. 2003;21:456–68. doi: 10.1016/S0738-081X(03)00058-0.
[30] De Braud F, Khayat D, Kroon BBR, Valdagni R, Bruzzi P, Casinelli N. Malignant melanoma. Crit Rev Oncol Hematol. 2003;47:35–63. doi: 10.1016/S1040-8428(02)00077-X.
Kwa RE, Campana K, Moy RL. Biology of cutaneous squamous cell carcinoma. J Am Acad Dermatol. 1999;41:443–8. doi: 10.1016/S0190-9262(99)70119-2.

Rippey JJ. Why classify basal cell carcinomas? Histopathology. 1998;32:393–8. doi: 10.1046/j.1365-2559.1998.00431.x.

Marur S, Forastiere AA. Head and neck squamous cell carcinoma: update on epidemiology, diagnosis, and treatment. Mayo Clin Proc. 2016;91:386–96. doi: 10.1016/j.mayocp.2015.12.017.

Guenthner ST, Hurwitz RM, Buckel LJ, Gray HR. Cutaneous squamous cell carcinomas consistently show histologic evidence of in situ changes: a clinicopathologic correlation. J Am Acad Dermatol. 1999;41:443–8. doi: 10.1016/S0190-9262(99)70119-2.

Drake LA, Ceilley RI, Cornelison RL, Dobes WA, Dorner W, Guenthner ST, Hurwitz RM, Buckel LJ, Gray HR. Cutaneous squamous cell carcinoma: update on epidemiology, diagnosis, and treatment. Mayo Clin Proc. 2016;91:386–96. doi: 10.1016/j.mayocp.2015.12.017.

Vantuchová Y, Číplík R. Histological types of basal cell carcinoma. Scr Medica Fac Medicae Univ Brun Masaryk. 2006;7:261–70.

Rippey JJ. Why classify basal cell carcinomas? Histopathology. 1998;32:393–8. doi: 10.1046/j.1365-2559.1998.00431.x.

Marur S, Forastiere AA. Head and neck squamous cell carcinoma: update on epidemiology, diagnosis, and treatment. Mayo Clin Proc. 2016;91:386–96. doi: 10.1016/j.mayocp.2015.12.017.

Guenthner ST, Hurwitz RM, Buckel LJ, Gray HR. Cutaneous squamous cell carcinomas consistently show histologic evidence of in situ changes: a clinicopathologic correlation. J Am Acad Dermatol. 1999;41:443–8. doi: 10.1016/S0190-9262(99)70119-2.

Rippey JJ. Why classify basal cell carcinomas? Histopathology. 1998;32:393–8. doi: 10.1046/j.1365-2559.1998.00431.x.

Marur S, Forastiere AA. Head and neck squamous cell carcinoma: update on epidemiology, diagnosis, and treatment. Mayo Clin Proc. 2016;91:386–96. doi: 10.1016/j.mayocp.2015.12.017.

Guenthner ST, Hurwitz RM, Buckel LJ, Gray HR. Cutaneous squamous cell carcinomas consistently show histologic evidence of in situ changes: a clinicopathologic correlation. J Am Acad Dermatol. 1999;41:443–8. doi: 10.1016/S0190-9262(99)70119-2.

Rippey JJ. Why classify basal cell carcinomas? Histopathology. 1998;32:393–8. doi: 10.1046/j.1365-2559.1998.00431.x.

Marur S, Forastiere AA. Head and neck squamous cell carcinoma: update on epidemiology, diagnosis, and treatment. Mayo Clin Proc. 2016;91:386–96. doi: 10.1016/j.mayocp.2015.12.017.

Guenthner ST, Hurwitz RM, Buckel LJ, Gray HR. Cutaneous squamous cell carcinomas consistently show histologic evidence of in situ changes: a clinicopathologic correlation. J Am Acad Dermatol. 1999;41:443–8. doi: 10.1016/S0190-9262(99)70119-2.

Rippey JJ. Why classify basal cell carcinomas? Histopathology. 1998;32:393–8. doi: 10.1046/j.1365-2559.1998.00431.x.

Marur S, Forastiere AA. Head and neck squamous cell carcinoma: update on epidemiology, diagnosis, and treatment. Mayo Clin Proc. 2016;91:386–96. doi: 10.1016/j.mayocp.2015.12.017.

Guenthner ST, Hurwitz RM, Buckel LJ, Gray HR. Cutaneous squamous cell carcinomas consistently show histologic evidence of in situ changes: a clinicopathologic correlation. J Am Acad Dermatol. 1999;41:443–8. doi: 10.1016/S0190-9262(99)70119-2.

Rippey JJ. Why classify basal cell carcinomas? Histopathology. 1998;32:393–8. doi: 10.1046/j.1365-2559.1998.00431.x.

Marur S, Forastiere AA. Head and neck squamous cell carcinoma: update on epidemiology, diagnosis, and treatment. Mayo Clin Proc. 2016;91:386–96. doi: 10.1016/j.mayocp.2015.12.017.

Guenthner ST, Hurwitz RM, Buckel LJ, Gray HR. Cutaneous squamous cell carcinomas consistently show histologic evidence of in situ changes: a clinicopathologic correlation. J Am Acad Dermatol. 1999;41:443–8. doi: 10.1016/S0190-9262(99)70119-2.

Rippey JJ. Why classify basal cell carcinomas? Histopathology. 1998;32:393–8. doi: 10.1046/j.1365-2559.1998.00431.x.

Marur S, Forastiere AA. Head and neck squamous cell carcinoma: update on epidemiology, diagnosis, and treatment. Mayo Clin Proc. 2016;91:386–96. doi: 10.1016/j.mayocp.2015.12.017.

Guenthner ST, Hurwitz RM, Buckel LJ, Gray HR. Cutaneous squamous cell carcinomas consistently show histologic evidence of in situ changes: a clinicopathologic correlation. J Am Acad Dermatol. 1999;41:443–8. doi: 10.1016/S0190-9262(99)70119-2.

Rippey JJ. Why classify basal cell carcinomas? Histopathology. 1998;32:393–8. doi: 10.1046/j.1365-2559.1998.00431.x.

Marur S, Forastiere AA. Head and neck squamous cell carcinoma: update on epidemiology, diagnosis, and treatment. Mayo Clin Proc. 2016;91:386–96. doi: 10.1016/j.mayocp.2015.12.017.

Guenthner ST, Hurwitz RM, Buckel LJ, Gray HR. Cutaneous squamous cell carcinomas consistently show histologic evidence of in situ changes: a clinicopathologic correlation. J Am Acad Dermatol. 1999;41:443–8. doi: 10.1016/S0190-9262(99)70119-2.
Nasir A. Nanodermatology: a bright glimpse just beyond the horizon.

Dianzani C, Zara GP, Maina G, Pettazzoni P, Pizzimenti S, Fuller CJ, Faulkner H, Bendich A, Parker RS, Roe DA. E

Parker RS, Roe DA. E

Shubayev VI, Pisanic TR, Jin S. Magnetic nanoparticles for skin care and dermatological treat

Dreher F, Gabard B, Schwindt DA, Maibach HI. Topical melatonin in combination with vitamins E and C protects skin from ultraviolet A

Marzuka AG, Book SE. Basal cell carcinoma: pathogenesis, management. Yale J Biol Med. 2015;88:167–79.

Fuller CJ, Faulkner H, Bendich A, Parker RS, Roe DA. Effect of β-carotene supplementation on photosuppression of delayed-type hypersensitivity in normal young men. Am J Clin Nutr. 1992;56:684–90. doi: 10.1093/ajcn/56.4.684.

Dreher F, Gabard B, Schwindt DA, Maibach HI. Topical melatonin in combination with vitamins E and C protects skin from ultraviolet A. Adv Drug Deliv Rev. 2011;63:470–91. doi: 10.1016/j.addr.2011.01.012.

Souza JJG, Gelfuso GM, Simão PS, Borges AC, Lopez RFV. Iontophoretic transport of zinc phthalocyanine tetrasulfonic acid as a tool to improve drug topical delivery. Anticancer Drugs. 2011;22:783–93. doi: 10.1097/CAD.0b013e3283468979.

Williams AC, Barry BW. Penetration enhancers. Adv Drug Deliv Rev. 2004;56:603–18. doi: 10.1016/j.addr.2003.10.025.

Diamanti C, Zara GP, Maina G, Pettazzoni P, Pizzimenti S, Rossi F, et al. Drug delivery nanoparticles in skin cancers. Biomed Res Int. 2014;2014:1–13. doi: 10.1155/2014/895986.

Shubayev VI, Pisaric TR, Jin S. Magnetic nanoparticles for theragnostics. Adv Drug Deliv Rev. 2009;61:467–77. doi: 10.1016/j.addr.2009.03.007.

Misak H, Zacharias N, Song Z, Hwang S, Man KP, Asmatulu R, et al. Skin cancer treatment by albumin/S-Fu loaded magnetic nanocomposite spheres in a mouse model. J Biotechnol. 2013;164:130–6. doi: 10.1016/j.jbiotec.2013.01.003.

Primo FL, Rodrigues MMA, Simioni AR, Bentley MVLB, Morais PC. In vitro studies of cutaneous retention of magnetic nanoemulsion loaded with zinc phthalocyanine for synergic use in skin cancer treatment. J Magn Magn Mater. 2008;320:e211–4. doi: 10.1016/j.jmmm.2008.02.050.

[79] Dorisuren B, Chaurasiya B, Ye Z, Liu Y, Li W, Wang C, et al. Cetuximab-coated thermo-sensitive liposomes loaded with magnetic nanoparticles and doxorubicin for targeted egf expressing breast cancer combined therapy. Int J Nanomed. 2020;15:8201–15. doi: 10.2147/IJN.S261671.

Akkarzadeh A, Rezaei-Sadabady R, Davaran S, Joo SW, Zarghami N, Hanifehpour Y, et al. Liposome: classification, preparation, and applications. Nanoscale Res Lett. 2013;8:102. doi: 10.1186/1556-276X-8-102.

Lukyanov AN, Elbayoumi TA, Chakilam AR, Torchilin VP. Tumor-targeted liposomes: doxorubicin-loaded long-circulating liposomes modified with anti-cancer antibody. J Control Rel. 2004;100:135–44. doi: 10.1016/j.jconrel.2004.08.007.

[81] Barenholz Y. Liposome application: problems and prospects. Curr Opin Colloid Interf Sci. 2001;6:66–77. doi: 10.1016/S0270-1207(00)00090-X.

Lasic DD. Liposomes in gene delivery. Boca Raton: CRC Press; 2019. doi: 10.1012/9780138748807.

Krieger ML, Eckstein N, Schneider V, Koch M, Royer HD, Jaedehe U, et al. Overcoming cisplatin resistance of ovarian cancer cells by targeted liposomes in vitro. Int J Pharm. 2010;389:10–7. doi: 10.1016/j.ijpharm.2009.12.061.

Abu Lila AS, Doi Y, Nakamura K, Ishida T, Shibata K, Kiwada H. Sequential administration with oxaliplatin-containing PEG-coated cationic liposomes promotes a significant delivery of subsequent dose into murine solid tumor. J Control Rel. 2010;142:167–73. doi: 10.1016/j.jconrel.2009.10.020.

Watanabe M, Kawano K, Toma K, Hattori Y, Maitani Y. In vivo antitumor activity of camptothecin incorporated in liposomes formulated with an artificial lipid and human serum albumin. J Control Rel. 2008;127:231–8. doi: 10.1016/j.jconrel.2008.02.005.

Kitagawa S, Kasamaki M. Enhanced delivery of retinoic acid to skin by cationic liposomes. Chem Pharm Bull. 2006;54:242–4. doi: 10.2322/jpsass.54.242.

El Zaafarany GM, Awad GS, Holayel SM, Mortada ND. Role of cationic liposomes in gene delivery. J Conjugate Anal Ther. 2006;54:242–4. doi: 10.2322/jpsass.54.242.

Connor A, Hawk J, Rafal E, Wolf P. E.

El Zaafarany GM, Awad GS, Holayel SM, Mortada ND. Role of cationic liposomes in gene delivery. J Conjugate Anal Ther. 2006;54:242–4. doi: 10.2322/jpsass.54.242.

Primard C, et al. Investigation of polylactic acid nanoparticles as drug delivery systems for local dermatotherapy. Pharm Res. 2009;26:2027–36. doi: 10.1007/s11095-009-9919-x.
Therapeutic strategies of AgNPs in the management of skin cancer

[92] Tuptal A, Sabzichi M, Ramezani F, Kouhsoltani M, Hamishehkar H. Dermal delivery of doxorubicin-loaded solid lipid nanoparticles for the treatment of skin cancer. J Microencapsul. 2016;33:372–80. doi: 10.1080/02652048.2016.1200150.

[93] Geetha T, Kapila M, Prakash O, Deol PK, Kakkar V, Kaur IP. Sesamol-loaded solid lipid nanoparticles for treatment of skin cancer. J Drug Target. 2015;23:159–69. doi: 10.3109/1061218X.2014.965717.

[94] Rigon RB, Fachinetti N, Severino P, Santana MHA, Chorilli M. Skin delivery and in vitro biological evaluation of trans-Resveratrol-Loaded solid lipid nanoparticles for skin disorder therapies. Molecules. 2016;21:116. doi: 10.3390/molecules21010116.

[95] Goto PL, Siqueira-Moura MP, Tedesco AC. Application of aluminum chloride phthalocyanine-loaded solid lipid nanoparticles for photodynamic inactivation of melanoma cells. Int J Pharm. 2017;518:228–41. doi: 10.1016/j.ijpharm.2017.01.004.

[96] Morton CA, Szeimies RM, Sidoroff A, Braathen LR. European guidelines for topical photodynamic therapy part 2: emerging indications – field carcinization, photorejuvenation and inflammatory/infective dermatoses. J Eur Acad Dermatol Venereol. 2013;27:672–9. doi: 10.1111/jdv.12026.

[97] Jang MS, Doh KS, Kang JS, Jeon YS, Suh KS, Kim ST. A comparative split-face study of photodynamic therapy with indocyanine green and indole-3-acetic acid for the treatment of acne vulgaris. Br J Dermatol. 2011;165:1095–1100. doi: 10.1111/j.1365-2133.2011.09722.x.

[98] Yang SJ, Shieh MJ, Lin FH, Lou PJ, Peng CL, Wei MF, et al. Colorrectal cancer cell detection by 5-aminolevulinic acid-loaded chitosan nano-particles. Cancer Lett. 2009;273:210–20. doi: 10.1016/j.canlet.2008.08.014.

[99] Li Y, Zhang W, Niu J, Chen Y. Surface-coating-dependent dissolution, aggregation, and reactive oxygen species (ROS) generation of silver nanoparticles under different irradiation conditions. Environ Sci Technol. 2013;47:10923–30. doi: 10.1021/es400945v.

[100] Rejiya CS, Kumar J, Raji V, Vibin M, Abraham A. Laser immunotherapy with gold nanorods causes selective killing of tumour cells. Pharmacol Res. 2012;65:261–9. doi: 10.1016/j.phrs.2011.10.005.

[101] Hadjikirova M, Troyanova P, Simeonova M. Nanoparticles as drug carrier system of 5-fluorouracil in local treatment of patients with superficial basal cell carcinoma. J BUON. 2005;10:517.

[102] Das S, Das J, Samadder A, Paul A, Khuda-Bukhsh AR. Efficacy of PLGA–loaded agiphenin nanoparticles in Benzo[a]pyrene and ultraviolet-B induced skin cancer of mice: mitochondria mediated apoptotic signalling cascades. Food Chem Toxicol. 2013;62:670–80. doi: 10.1016/j.fct.2013.09.037.

[103] Iwasaki JK, Srivastava D, Moy RL, Lin HJ, Kouba DJ. The molecular genetics underlying basal cell carcinoma pathogenesis and links to targeted therapeutics. J Am Acad Dermatol. 2012;66:e167–78. doi: 10.1016/j.jaad.2010.06.054.

[104] Huang X, El-Sayed MA. Gold nanoparticles: optical properties and implementations in cancer diagnosis and photothermal therapy. J Adv Res. 2010;1:13–28. doi: 10.1016/j.jare.2010.02.002.

[105] Huang X, El-Sayed IH, Qian W, El-Sayed MA. Cancer cell imaging and photothermal therapy in the near-infrared region by using gold nanorods. J Am Chem Soc. 2006;128:2115–20. doi: 10.1021/ja057254a.

[106] Sokolov K, Follen M, Aaron J, Pavlova I, Malpica A, Lotan R, et al. Real-time optical imaging of precancer using anti-epidermal growth factor receptor antibodies conjugated to gold nanoparticles. Cancer Res. 2003;63:2115–20.

[107] Baroli B, Ennas MG, Loffredo F, Isola M, Pinna R, López-Quintela MA. Penetration of metallic nanoparticles in human full-thickness skin. J Invest Dermatol. 2007;127:1701–12. doi: 10.1038/sj.jid.5700733.

[108] Li J, Wang J, Wang Y, Trau M. Simple and rapid colorimetric detection of melanoma circulating tumor cells using bifunctional magnetic nanoparticles. Analyst. 2017;142:4788–93. doi: 10.1039/c7an0102d.

[109] Loo C, Lowery A, Halas N, West J, Drezek R. Immunotargeted nanoshells for integrated cancer imaging and therapy. Nano Lett. 2005;5:709–11. doi: 10.1021/nl050127s.

[110] Kneipp K, Kneipp H, Itzkau I, Dasari RR, Feld MS. Surface-enhanced Raman scattering and biophysics. J Phys Condens Matter. 2002;14:R597–R624. doi: 10.1088/0953-8984/14/18/202.

[111] Kang H, Jeong S, Park Y, Yim J, Jun BH, Kyeong S, et al. Near-infrared SERS nanoprobes with plasmonic AuAg hollow-shell assemblies for in vivo multiplex detection. Adv Funct Mater. 2013;23:3719–27. doi: 10.1002/adfm.201203726.

[112] Huang X, El-Sayed IH, Qian W, El-Sayed MA. Cancer cells assemble and align gold nanorods conjugated to antibodies to produce highly enhanced, sharp, and polarized surface Raman spectra: a potential cancer diagnostic marker. Nano Lett. 2007;7:1591–7. doi: 10.1021/nl070472c.

[113] Kim JH, Kim JS, Choi H, Lee SM, Jun BH, Yu KN, et al. Nanoparticle probes with surface enhanced Raman spectroscopic tags for cellular cancer targeting. Anal Chem. 2006;78:6967–73. doi: 10.1021/ac0607663.

[114] Lee S, Chon H, Lee M, Choo J, Shin SY, Lee YH, et al. Surface-enhanced Raman scattering imaging of HER2 cancer markers overexpressed in single MCF7 cells using antibody conjugated hollow gold nanospheres. Biosens Bioelectron. 2009;24:2260–3. doi: 10.1016/j.bios.2008.10.018.

[115] Qian X, Peng XH, Anserdi DQ, Yin-Goen Q, Chen GZ, Shin DM, et al. In vivo tumor targeting and spectroscopic detection with surface-enhanced Raman nanoparticle tags. Nat Biotechnol. 2008;26:83–90. doi: 10.1038/nbt1377.

[116] Lee S, Kim S, Choo J, Shin SY, Lee YH, Choi HY, et al. Biological imaging of HEK293 cells expressing PLC[41] using surface-enhanced Raman microscopy. Anal Chem. 2007;79:916–22. doi: 10.1021/ac061246a.

[117] Schlücker S, Kümpfe K, Gellner M. Multiplexing with SERS labels using mixed SAMs of raman reporter molecules. Analytical Chem. 2006;78:73–80. doi: 10.1021/ac051809v.

[118] Burdușel AC, Gherasim O, Grumesescu AM, Mogoanta L, Ficai A, Andronescu E. Biomedical applications of silver nanoparticles: an up-to-date overview. Nanomaterials. 2018;8:681. doi: 10.3390/nano8090681.

[119] Edwards-Jones V. The benefits of silver in hygiene, personal care and healthcare. Lett Appl Microbiol. 2009;49:147–52. doi: 10.1111/j.1472-765X.2009.02648.x.

[120] Liu J, Jiang G. Silver nanoparticles in the environment. Berlin: Springer; 2015. doi: 10.1007/978-3-662-46070-2.
Panáček A, Kvítek L, Smékalová M, Večerňová R, Kolář M, Röderová M, et al. Bacterial resistance to silver nanoparticles and how to overcome it. Nat Nanotechnol. 2018;13:65–71. doi: 10.1038/s41565-017-0033-y.

Otari SV, Patil RM, Ghosh SJ, Thorat ND, Pawar SH. Intracellular synthesis of silver nanoparticle by actinobacteria and its antimicrobial activity. Spectrochim Acta Part A Mol Biomol Spectrosc. 2015;136:1175–80. doi: 10.1016/j.saa.2014.10.003.

Xu L, Wang YY, Huang J, Chen CY, Wang ZX, Xie H. Silver nanoparticles: synthesis, medical applications and bio-safety. Theranostics. 2020;10:8996–9031. doi: 10.7150/thno.45413.

Eom HJ, Choi J. p38 MAPK activation, DNA damage, cell cycle arrest and apoptosis as mechanisms of toxicity of silver nanoparticles in Jurkat T cells. Envi Sci Technol. 2010;44:8337–42. doi: 10.1021/es1020668.

Tian J, Wong KKY, Ho CM, Lok CN, Yu WY, Che CM, et al. Topical delivery of silver nanoparticles promotes wound healing. Chem Med Chem. 2007;2:129–36. doi: 10.1002/cmdc.200600171.

Marsich E, Bellomo F, Turco G, Travani A, Donati I, Paolotti S. Nano-composite scaffolds for bone tissue engineering containing silver nanoparticles: preparation, characterization and biological properties. J Mater Sci Mater Med. 2013;24:1799–807. doi: 10.1007/s10856-013-4923-4.

Qing T, Mahmood M, Zheng Y, Biris AS, Shi L, Casciano DA. A genomic characterization of the influence of silver nanoparticles on bone differentiation in MC3T3-E1 cells. J Appl Toxicol. 2018;38:172–9. doi: 10.1007/jat.3528.

Velusamy P, Su CH, Venkat Kumar G, Adhikary S, Pandian K, Gopinath SCB, et al. Biopolymers regulate silver nanoparticle under microwave irradiation for effective antibacterial and antibiofilm activities. PLoS One. 2016;11:e0157612. doi: 10.1371/journal.pone.0157612.

Cohan R, Shoari A, Baghbani-Arani F, Shandiz AS, Khosravi MS, Janani A, et al. Green synthesis and evaluation of silver nanoparticles as adjuvant in rabbits veterinary vaccine. Int J Nanomed. 2016;11:3597–605. doi: 10.2147/IJN.S109098.

Saratole GD, Saratole RG, Benelli G, Kumar G, Pugazhendhi A, Kim DS, et al. Anti-diabetic potential of silver nanoparticles synthesized with Argyreia nervosa leaf extract high synergistic antibacterial activity with standard antibiotics against foodborne bacteria. J Clust Sci. 2017;28:1709–27. doi: 10.1007/s10876-017-1179-2.

Lee SH, Jun BH. Silver nanoparticles: synthesis and application for nanomedicine. Int J Mol Sci. 2019;20:865. doi: 10.3390/ijms20040865.

Mulvaney SP, Musick MD, Keating CD, Natan MJ. Glass-coated analyte-tagged nanoparticles: a new tagging system based on detection with surface-enhanced Raman scattering. Langmuir. 2003;19:4784–90. doi: 10.1021/la026706j.

Doering WE, Piotti ME, Natan MJ, Freeman RG. SERS as a foundation for nanoscale, optically detected biological labels. Adv Mater. 2007;19:3100–8. doi: 10.1002/adma.200701984.

Camen J, Dieringer JA, Wang Y, Masiello DJ, Marks LD, Schatz GC, et al. Probing the structure of single-molecule surface-enhanced Raman scattering hot spots. J Am Chem Soc. 2008;130:12616–7. doi: 10.1021/ja8051427.

Jun BH, Noh MS, Kim J, Kim G, Kang H, Kim MS, et al. Multifunctional silver-embedded magnetic nanoparticles as SERS nanoprobes and their applications. Small. 2010;6:119–25. doi: 10.1002/smll.200901459.

Haes AJ, Hall WP, Chang L, Klein WL, Van, Duyne RP. A localized surface plasmon resonance biosensor: first steps toward an assay for Alzheimer’s disease. Nano Lett. 2004;4:1029–34. doi: 10.1021/nl0409670j.

Zhou W, Ma Y, Yang H, Ding Y, Luo X. A label-free biosensor based on silver nanoparticles array for clinical detection of serum p53 in head and neck squamous cell carcinoma. Int J Nanomed. 2011;6:381. doi: 10.2147/ijn.s13249.

Yen CW, De Puig H, Tan JO, Gómez-Márquez J, Bosch I, Hamad-Schifferli K, et al. Multicolored silver nanoparticles for multiplexed disease diagnostics: distinguishing dengue, yellow fever, and Ebola viruses. Lab Chip. 2015;15:1638–41. doi: 10.1039/c5lc00055f.

Malicka J, Grynzynski I, Lakowicz JR. DNA hybridization assays using metal-enhanced fluorescence. Biochem Biophys Res Commun. 2003;306:213–8. doi: 10.1016/S0006-291X(03)00935-5.

Aslan K, Lakowicz JR, Szmaczinski H, Geddes CD. Enhanced ratiometric pH sensing using SNAFL-2 on silver Island films: metal-enhanced fluorescence sensing. J Fluoresc. 2005;15:37–40. doi: 10.1007/s10895-005-0211-0.

Aslan K, Grynzynski I, Malicka J, Matveeva E, Lakowicz JR, Geddes CD. Metal-enhanced fluorescence: an emerging tool in biotechnology. Curr Opin Biotechnol. 2005;16:55–62. doi: 10.1016/j.copbio.2005.01.001.

Larese FF, D’Agostin F, Crosera M, Adami G, Renzi N, Bovenzi M, et al. Human skin penetration of silver nanoparticles through intact and damaged skin. Toxicology. 2009;255:33–40. doi: 10.1016/j.tox.2008.09.025.

George R, Merten S, Wang TT, Kennedy P, Maitz P. In vivo analysis of dermal and systemic absorption of silver nanoparticles through healthy human skin. Australas J Dermatol. 2014;55:185–90. doi: 10.1111/ajd.12101.

Samberg ME, Oldenburg SJ, Monteiro-Riviere NA. Evaluation of silver nanoparticle toxicity in skin in vivo and keratinocytes in vitro. Environ Health Perspect. 2010;118:407–13. doi: 10.1289/ehp.0901398.

Verano-Braga T, Miethling-Graff R, Wojdyla K, Rogowska-Wrezinska A, Brewer JR, Erdmann H, et al. Insights into the cellular response triggered by silver nanoparticles using quantitative proteomics. ACS Nano. 2014;8:2161–75. doi: 10.1021/nn4050744.

Kokura S, Hando O, Takagi T, Ishikawa T, Naito Y, Yoshikawa T. Silver nanoparticles as a safe preservative for use in cosmetics. Nanomed Nanotechnol Biol Med. 2010;6:570–4. doi: 10.1016/j.nano.2009.12.002.

Liu X, Lee P, Ho C, Lui VCH, Chen Y, Che C, et al. Silver nanoparticles mediate differential responses in keratinocytes and fibroblasts during skin wound healing. Chem Med Chem. 2010;5:468–75. doi: 10.1002/cmdc.20090502.

Kwan KH, Liu X, To MK, Yeung KW, Ho CM, Wong KK. Modulation of collagen alignment by silver nanoparticles results in better mechanical properties in wound healing.
Therapeutic strategies of AgNPs in the management of skin cancer

[149] Wei L, Lu J, Xu H, Patel A, Chen ZS, Chen G. Silver nanoparticles: synthesis, properties, and therapeutic applications. Drug Discov Today. 2015;20:595–601. doi: 10.1016/j.drudis.2014.11.014.

[150] Abou El-Nour KMM, Elfaiha A, Al-Warthan A, Ammar RAA. Synthesis and applications of silver nanoparticles. Arab J Chem. 2010;3:135–40. doi: 10.1016/j.arabjc.2010.04.008.

[151] Johnston HJ, Hutchison G, Christensen FM, Peters S, Hankin S, Stone V. A review of the in vivo and in vitro toxicity of silver and gold particulates: particle attributes and biological mechanisms responsible for the observed toxicity. Crit Rev Toxicol. 2010;40:328–46. doi: 10.3109/10408440903453074.

[152] Ryceenga M, Coblentz CM, Zeng J, Li W, Moran CH, Zhang Q, et al. Controlling the synthesis and assembly of silver nanostructures for plasmonic applications. Chem Rev. 2011;111:3669–712. doi: 10.1021/cr100275d.

[153] Powers CM, Badireddy AR, Ryde IT, Seidler FJ, Slocotn TA. Silver nanoparticles compromise neurodevelopment in PC12 cells: critical contributions of silver ion, particle size, coating, and composition. Environ Health Perspect. 2011;119:37–44. doi: 10.1289/ehp.1102337.

[154] Schäfer Korting M, Mehnert W, Korting HC. Lipid nanoparticles for in vitro and in vivo delivery of paclitaxel to induce HepG2 cell apoptosis. Int J Nanotechnol. 2010;7:6693–702. doi: 10.2147/IJN.S122666.

[155] Zhang T, Wang L, Chen Q, Chen C. Cytotoxic potential of silver nanoparticles: chemical, physical and biological methods. Res Pharm Sci. 2014.

[156] Li Y, Guo M, Lin Z, Zhao M, Xiao M, Wang C, et al. Polyethyleneimine-functionalized silver nanoparticle-based co-delivery of paclitaxel to induce HepG2 cell apoptosis. Int J Nanomed. 2016;11:6693–702. doi: 10.2147/IJN.S122666.

[157] Asha Rani PV, Mun GLK, Hande MP, Valiyaveettil S. Cytotoxicity and genotoxicity of silver nanoparticles in human cells. ACS Nano. 2009;3:279–90. doi: 10.1021/nn800596w.

[158] Vimala HS, Libin J, Malamud S, Blackwood R, Selvarajah K, et al. Silver nanoparticles induce apoptosis in A549 cells and inhibit lung cancer cell migration in vivo. Arch Toxicol. 2011;85:743–50. doi: 10.1007/s00204-010-0545-5.

[159] Jogeshwar A, Vidyarani B, Jayasree S, et al. Nanostructured silver nanoparticles with improved cytotoxicity and myristic acid functionalization for cancer therapy. Nat Mater. 2013;12:570–76. doi: 10.1038/nmat3577.

[160] Rajasekaran S, Karthikeyan S, et al. Development and characterization of silver nanoparticles: a review. Int J Nanomedicine. 2012;7:497–504. doi: 10.2147/IJN.S130814.

[161] Akter M, Sikder MT, Rahman MM, Ullah AKMA, Hossain KFB, et al. Controlling the synthesis and assembly of silver nanoparticles: size, coating, and composition. Environ Health Perspect. 2011;119:37–44. doi: 10.1289/ehp.1102337.

[162] Shamsuzzoha M, Ooi C, Kruizinga R. Silver nanoparticles: promising therapeutic agents for cancer treatment. Nat Rev Drug Discov. 2013;12:101–13. doi: 10.1038/nrd3917.

[163] Amita S, Singh VK, Prasad Y, Singh R, et al. Silver nanoparticles: a review on a versatile nanomaterial for cancer therapy. J Nanoparticle Res. 2013;15:118.

[164] Zhang T, Wang L, Chen Q, Chen C. Cytotoxic potential of silver nanoparticles: chemical, physical and biological methods. Res Pharm Sci. 2014.

[165] Asha Rani PV, Mun GLK, Hande MP, Valiyaveettil S. Cytotoxicity and genotoxicity of silver nanoparticles in human cells. ACS Nano. 2009;3:279–90. doi: 10.1021/nn800596w.

[166] Li Y, Guo M, Lin Z, Zhao M, Xiao M, Wang C, et al. Polyethyleneimine-functionalized silver nanoparticle-based co-delivery of paclitaxel to induce HepG2 cell apoptosis. Int J Nanomed. 2016;11:6693–702. doi: 10.2147/IJN.S122666.

[167] Zhang T, Tooyooka T, Ibuki Y. Silver nanoparticle-induced phosphorylation of histone H3 at serine 10 is due to dynamic changes in actin filaments and the activation of Aurora kinases. Toxicol Lett. 2017;276:39–47. doi: 10.1016/j.toxlet.2017.05.009.

[168] Iravani S, Korbekandi H, Mirmohammadi SV, Zolfaghari B. Synthesis of silver nanoparticles: chemical, physical and biological methods. Res Pharm Sci. 2014.

[169] Carvalho SM, Mansur AAP, Capanova NSV, Carvalho ICL, Chagas P, de Oliveira LCA, et al. Synthesis and in vitro assessment of anticancer hydrogels composed by carboxymethylcellulose-doxorubicin as potential transdermal delivery systems for treatment of skin cancer. J Mol Liq. 2018;266:425–40. doi: 10.1016/j.molliq.2018.06.085.

[170] Liu Y, Sheikh MS. Melanoma: molecular pathogenesis and therapeutic management. Mol Cell Pharmacol. 2014;6:228. doi: 10.4255/mcp Pharmacol.14.03.

[171] Pal S, Tak YK, Song JM. Does the antibacterial activity of silver nanoparticles depend on the shape of the nanoparticle? A study of the gram-negative bacterium Escherichia coli. Appl Env Microbiol. 2007;73:1712–20. doi: 10.1128/AEM.02218-06.

[172] Carlson C, Hussain SM, Schrand AM, K. Braydich-Stolle L, Hess KL, Jones RL, et al. Unique cellular interaction of silver nanoparticles: size-dependent generation of reactive oxygen species. J Phys Chem B. 2008;112:33608–19. doi: 10.1021/jp712087m.

[173] Kvitek L, Vanickova M, Panacek A, Soukupova J, Dittrich M, Valentova E, et al. Initial study on the toxicity of silver nanoparticles which pass through the human skin. Int J Nanomedicine. 2016;11:7553–64. doi: 10.2147/IJN.S102194.

[174] Capanova NSV, Carvalho ICL, Mansur AAP, Carvalho SM, Lage AP, Mansur HS. Hybrid hydrogel composed of carboxymethylcellulose-silver nanoparticles-doxorubicin for anticancer and antibacterial therapies against melanoma skin cancer cells. ACS Appl Mater Interfaces. 2019;11:90. doi: 10.1021/acsami.9b01924.

[175] Cancer Quest: Cervical cancer | Cancer Quest. Emory, Winship Cancer Institute.

[176] Jain V, Jain S, Mahajan SC. Nanomedicines based drug delivery systems for anti-cancer targeting and treatment. Curr Drug Deliv. 2015;12:779–91. doi: 10.2174/1567201811666410822112516.

[177] Ahkit MA, Rizwanullah M, Ahmad J, Ahsan MJ, Mujtaba MA, Amin S. Nanocarriers in advanced drug targeting: setting
novel paradigm in cancer therapeutics. Artif Cells Nanomed Biotechnol. 2018;46:873–84. doi: 10.1080/21691401.2017.1366333.

[178] Medina O, Zhu Y, Kairemo K. Targeted liposomal drug delivery in cancer. Curr Pharm Des. 2005;10:2981–9. doi: 10.2174/1381612043383467.

[179] Peram MR, Jalalpure S, Kumbar V, Patil S, Joshi S, Bhat K, et al. Factorial design based curcumin ethosomal nanocarriers for the skin cancer delivery: in vitro evaluation. J Liposome Res. 2019;29:291–311. doi: 10.1080/08982104.2018.1556292.

[180] Boakye CHA, Patel K, Doddapaneni R, Bagde A, Behl G, Chowdhury N, et al. Ultra-flexible nanocarriers for enhanced topical delivery of a highly lipophilic antioxidative molecule for skin cancer chemoprevention. Colloids Surf B Biointerf. 2016;143:156–67. doi: 10.1016/j.colsurfb.2016.03.036.

[181] Kang L, Gao Z, Huang W, Jin M, Wang Q. Nanocarrier-mediated co-delivery of chemotherapeutic drugs and gene agents for cancer treatment. Acta Pharm Sin B. 2015;5:169–75. doi: 10.1016/j.apsb.2015.03.001.

[182] Bonifácio BV, da Silva PB, Aparecido dos Santos Ramos M, Maria Silveira Negri K, Maria Bauab T, Chorilli M. Nanotechnology-based drug delivery systems and herbal medicines: a review. Int J Nanomed. 2013;9:1. doi: 10.2147/ijn.2013.352634.

[183] Guo J, Xing C, Yuan H, Chai R, Zhan Y. Oligo-(p-phenylene vinylene)/polyisocyanoazobiphenyl composite hydrogel-based three-dimensional cell culture system for anticancer and antibacterial therapies. ACS Biomater Sci Eng. 2019;5:2520–7. doi: 10.1021/acsabi.9b00217.

[184] Tang JQ, Hou XY, Yang CS, Li YX, Xin Y, Guo WW, et al. Recent developments in nanomedicine for melanoma treatment. Int J Cancer. 2017;141:646–53. doi: 10.1002/ijc.30708.

[185] Huynh KA, Chen KL. Aggregation kinetics of citrate and polyvinylpyrrolidone coated silver nanoparticles in monovalent and divalent electrolyte solutions. Env Sci Technol. 2011;45:5564–71. doi: 10.1021/es200157h.

[186] Liu J, Zhao Y, Guo Q, Wang Z, Wang H, Yang Y, et al. TAT-modified nanosilver for combating multidrug-resistant cancer. Biomaterials. 2012;33:6155–61. doi: 10.1016/j.biomaterials.2012.05.035.

[187] Kawata K, Osawa M, Okabe S. In vitro toxicity of silver nanoparticles at noncytotoxic doses to HepG2 human hepatoma cells. Env Sci Technol. 2009;43:6046–51. doi: 10.1021/es900754q.

[188] Ibrahim WN, Muizzuddin Bin Mohd Rosli L, Doolaan AA. Formulation, cellular uptake and cytotoxicity of thymoquinone-loaded plga nanoparticles in malignant melanoma cancer cells. Int J Nanomed. 2020;15:8059–74. doi: 10.2147/ijn.5269340.

[189] Powers CM, Slotkin TA, Seidler FJ, Badreddy AR, Padilla S. Silver nanoparticles alter zebrafish development and larval behavior: distinct roles for particle size, coating and composition. Neurotoxicol Teratol. 2011;33:708–14. doi: 10.1016/j.ntt.2011.02.002.

[190] Malik MA, O’Brien P, Revaprasadu N. A simple route to the synthesis of core/shell nanoparticles of chalcogenides. Chem Mater. 2002;14:2004–10. doi: 10.1021/cm011154w.

[191] Netchareonsirisuk P, Puthong S, Dubas S, Palaga T, Komolpis K. Effect of capping agents on the cytotoxicity of silver nanoparticles in human normal and cancer skin cell lines. J Nanopart Res. 2016;18:322. doi: 10.1007/s11051-016-3624-6.

[192] Gurunathan S, Kalishwaralal K, Vaidyanathan R, Venkataaraman D, Pandian SRK, Muniraj J, et al. Biosynthesis, purification and characterization of silver nanoparticles using Escherichia coli. Colloids Surf B Biointerf. 2009;74:328–35. doi: 10.1016/j.colsurfb.2009.07.048.

[193] Mousavi SM, Hashemi SA, Ghasemi Y, Atapour A, Amani AM, Savar Dashtaki A, et al. Green synthesis of silver nanoparticles toward bio and medical applications: review study. Artif Cells Nanomed Biotechnol. 2018;46:585–72. doi: 10.1080/21691401.2018.1517769.

[194] Kalimuthu K, Vijayakumar S, Senthilkumar R. Antimicrobial activity of the biodiesel plant, Jatropha curcas L. Int J Pharma Bio Sci. 2010;1:1–5.

[195] Ahn YJ, Jin H, Park Y. Green synthesis and biological activities of silver nanoparticles prepared by Carpesium cernuum extract. Arch Pharm Res. 2019;42:926–34. doi: 10.1007/s12272-019-01152-x.

[196] Abdellah AM, Sliem MA, Bakr M, Amin RM. Green synthesis and biological activity of silver-curcumin nanocomjugates. Future Med Chem. 2018;10:2577–88. doi: 10.4155/fmc-2018-0152.

[197] Goyal S, Gupta N, Kumar A, Chatterjee S, Nimesh S. Antibacterial, anticancer and antioxidant potential of silver nanoparticles engineered using trigonella foenum-graecum seed extract. IET Nanobiotechnol. 2018;12:526–33. doi: 10.1049/iet-nbt.2017.0089.

[198] Nayak D, Pradhan S, Ashe S, Rauta PR, Nayak B. Biologically synthesised silver nanoparticles from three diverse family of plant extracts and their anticancer activity against epidermoid A431 carcinoma. J Colloid Interf Sci. 2015;457:329–38. doi: 10.1016/j.jcis.2015.07.012.

[199] Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364:2507–16. doi: 10.1056/nejmoa1103782.

[200] Sanlorenzo M, Choudhry A, Vujic I, Posch C, Chong K, Johnston K, et al. Comparative profile of cutaneous adverse events: BRAF/MEK inhibitor combination therapy versus BRAF monotherapy in melanoma. J Am Acad Dermatol. 2014;71:1102–e1. doi: 10.1016/j.jaad.2014.09.002.

[201] Sullivan RJ, Weber JS, Patel SP, Dummer R, Miller WH, Cosgrove D, et al. A phase I/II study of BRAF inhibitor (BRAFi) encorafenib (ENCO) plus MEK inhibitor (MEKI) binimetinib (BINI) in cutaneous melanoma patients naïve to BRAFi therapy. J Clin Oncol. 2015;33:9007. doi: 10.1200/jco.2015.33.15_suppl.9007.

[202] Falchook GS, Lewis KD, Infante JR, Gordon MS, Vogelzang NJ, DeMarini DJ, et al. Activity of the oral MEK inhibitor trametinib (ENCO) in patients with advanced melanoma: a phase 1 dose-escalation trial. Lancet Oncol. 2012;13:782–9. doi: 10.1016/s1470-2045(12)70269-3.

[203] Signorelli J, Shah Gandhi A. Cobimetinib: a novel MEK inhibitor for metastatic melanoma. Ann Pharmacother. 2017;51:146–53. doi: 10.1177/1060028016672037.

[204] Dummer R, Schadendorf D, Ascierto PA, Arance A, Dutriaux C, Di Giacomo AM, et al. Binimetinib versus dacarbazine in
patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2017;18:435–45. doi: 10.1016/S1470-2245(17)30180-8.

[205] Lipson EJ, Drake CG. Ipilimumab: an anti-CTLA-4 antibody for metastatic melanoma. Clin Cancer Res. 2011;17:6958–62. doi: 10.1158/1078-0432.CCR-11-1595.

[206] Brahmer JR, Hammers H, Lipson EJ. Nivolumab: targeting PD-1 to bolster antitumor immunity. Futur Oncol. 2015;11:1307–26. doi: 10.2217/fon.15.52.

[207] Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015;372:2521–32. doi: 10.1056/NEJMoa1503093.

[208] Ramsay JR, Suhrbier A, Aylward JH, Ogbourne S, Cozzi SJ, Poulsen MG, et al. The sap from Euphorbia peplus is effective against human nonmelanoma skin cancers. Br J Dermatol. 2011;164:633–6. doi: 10.1111/j.1365-2133.2010.10184.x.

[209] Kacerovská D, Pizinger K, Majer F, Šmíd F. Photodynamic therapy of nonmelanoma skin cancer with topical Hypericum perforatum extract – a pilot study. Photochem Photobiol. 2008;84:779–85. doi: 10.1111/j.1751-1097.2007.00260.x.

[210] Stensvold I, Jacobsen BK. Coffee and cancer: a prospective study of 43,000 Norwegian men and women. Cancer Causes Control. 1994;5:401–8. doi: 10.1007/BF01694753.

[211] Asgari MM, White E, Warton EM, Hararah MK, Friedman GD, Chen MM. Association of tea consumption and cutaneous squamous cell carcinoma. Nutr Cancer. 2011;63:314–8. doi: 10.1080/01635581.2011.523496.

[212] Huang MT, Ma W, Lu YP, Chang RL, Fisher C, Manchand PS, et al. Effects of curcumin, demethoxycurcumin, bisde-methoxycurcumin and tetrahydrocurcumin on 12-O-tetradecanoylphorbol-13-acetateinduced tumor promotion. Carcinogenesis. 1995;16:2493–7. doi: 10.1093/carcin/16.10.2493.

[213] Wei H, Salardi R, Lu Y, Wang Y, Palep SR, Moore J, et al. Isoflavone genistein: photoprotection and clinical implications in dermatology. J Nutr. 2003;133:3811S–9S. doi: 10.1093/jn/133.11.3811s.

[214] Mittal A, Elmets CA, Katiyar SK. Dietary feeding of proanthocyanidins from grape seeds prevents photocarcinogenesis in SKH-1 hairless mice: relationship to decreased fat and lipid peroxidation. Carcinogenesis. 2003;24:1379–88. doi: 10.1093/carcin/bgg095.

[215] Rizwan M, Rodríguez-Blanco I, Harbottle A, Birch-Machin MA, Watson REB, Rhodes LE. Tomato paste rich in lycopene protects against cutaneous photodamage in humans in vivo: a randomized controlled trial. Br J Dermatol. 2011;164:154–62. doi: 10.1111/j.1365-2133.2010.10057.x.