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NANO-DRUG DELIVERY SYSTEMS ENTRAPPING NATURAL BIOACTIVE COMPOUNDS FOR SKIN CANCER: RECENT PROGRESS AND FUTURE CHALLENGES

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ABSTRACT
Cancer remains a significant global health challenge, with skin cancer being one of the most prevalent types. Traditional treatments often face limitations, including severe side effects due to the lack of tumor selectivity in many chemotherapeutic agents. This paper explores the potential of nano-drug delivery systems that incorporate natural bioactive compounds for the treatment of skin cancer. By leveraging the unique properties of nanoparticles, such as enhanced solubility, stability, and targeted delivery, these systems can improve therapeutic efficacy while minimizing adverse effects. The role of Ayurvedic medicine and its use of phytochemicals is highlighted, emphasizing the importance of integrating traditional knowledge with modern nanotechnology. The review discusses various types of nanoparticles and herbal formulations that enhance drug delivery and presents a promising approach to optimizing skin cancer treatments. Future challenges in this field include further research on safety, efficacy, and the pharmacological validation of Ayurvedic practices. Overall, the combination of natural compounds with advanced nanotechnology offers a novel pathway to improve outcomes in skin cancer therapy.

KEYWORDS: Skin Cancer, Ayurveda, Phytoconstituents, Nanotechnology, Bioactive.

INTRODUCTION
Cancer is a condition characterized by uncontrolled cell growth that can spread to vital organs through processes such as invasion, angiogenesis, and distant metastasis.[1] Cancer ranks as the second leading cause of death and poses a significant public health challenge globally.[2] Cancer is a distressing illness that can lead to pain, disfigurement, and disruption of various bodily functions. It can develop at any age and affect any part of the body.[3] Noncommunicable diseases (NCDs) are now the leading cause of death worldwide, with cancer anticipated to become the primary cause of mortality and a major obstacle to improving life expectancy in every country this century. According to 2015 estimates from the World Health Organization (WHO), cancer is the leading or second leading cause of death before age 70 in 91 out of 172 countries, and it ranks third or fourth in an additional 22 countries.[4] Cancer encompasses a range of types marked by unchecked cell growth. Common forms include breast cancer, lung cancer, prostate cancer, and colorectal cancer. Skin cancers, such as melanoma, along with blood cancers like leukemia and lymphoma, are also notable. Each type presents unique risk factors, symptoms, and treatment strategies, highlighting the complexity of the disease.[5]

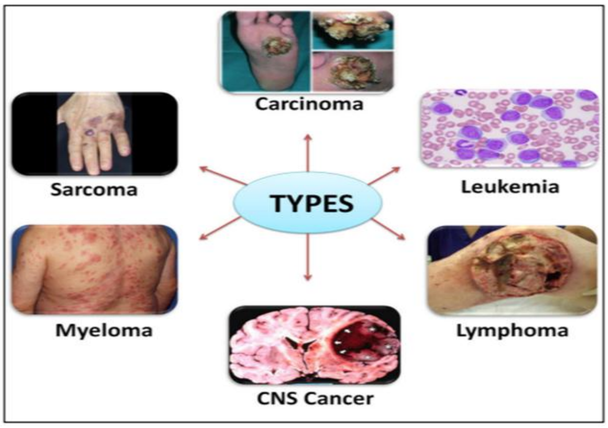

Fig.1 Types of Skin Cancer.

Regular exposure to carcinogens like tobacco, ultraviolet light, and certain infections can result in various genetic mutations, epigenetic changes (such as loss of heterozygosity), and alterations in the transcriptome, often through inflammation pathways. These factors are associated with a heightened risk of developing cancer.[6] Extended exposure to radiation, contact with harmful chemicals, and recurrent injuries can contribute to the development of skin cancer.[7] Among the different types of skin cancer, the incidence of clinically severe melanoma is approximately twice as high in men compared to women.[8] Several treatment strategies are used for melanoma, including surgery, photodynamic therapy, immunotherapy, virotherapy, targeted therapy, drug therapy, radiation therapy, and chemotherapy.[9] A significant drawback of anticancer drugs is their lack of selectivity for tumor tissue, leading to severe side effects and often resulting in low cure rates.[10]

Plants produce secondary metabolites that exhibit anticancer potential for clinical drug development. Additionally, using nanocarriers can enhance the solubility and stability of these phytocompounds, allowing for targeted delivery to specific sites.[11]

SKIN CANCER

Skin cancer is diagnosed in about 3 million Americans annually, making it one of the most prevalent types of cancer in the country and globally. While it is common, skin cancer accounts for approximately 1 percent of all cancer-related deaths worldwide.[12] Skin: a challenging barrier. Covering approximately 1.8 square meters, the skin is the largest and most extensive organ in the body. It consists of three primary layers: the epidermis, dermis, and subcutaneous tissue, which include structures like hair follicles and sebaceous glands. The outermost layer is the epidermis.[13] Skin cancers make up about 20% of non-melanocytic skin cancers.[14] The primary types of skin cancer are melanoma, basal cell carcinoma, and squamous cell carcinoma.[15] Squamous cell carcinoma (SCC) is one of the most prevalent skin cancers, while melanoma is among the most serious forms and ranks as the 19th most common cancer worldwide.[16] Melanoma is the most common skin cancer in humans, and treatment options often include chemotherapy, radiotherapy, surgery, or a combination of these modalities.[17]

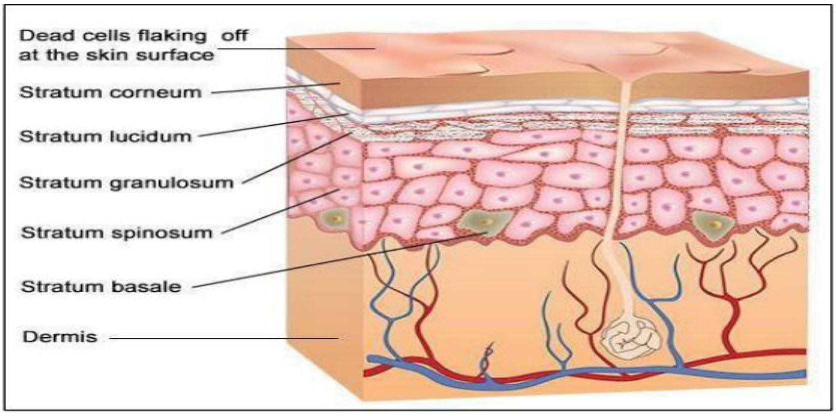

Fig. 2 Structure of Skin.

Skin cancer (SC) originates from abnormal cell proliferation in the epidermis, the outer layer of the skin. This process is triggered by unrepaired DNA damage, which activates mutations and leads to rapid proliferation of skin cells, resulting in the formation of malignant tumors.[18] It refers to a pathological condition marked by the uncontrolled proliferation of atypical skin cells.[19] The most common type of cancer worldwide is characterized by the uncontrolled growth of abnormal cells in the epidermis, which is triggered by unrepaired DNA damage that results in mutations.[20]

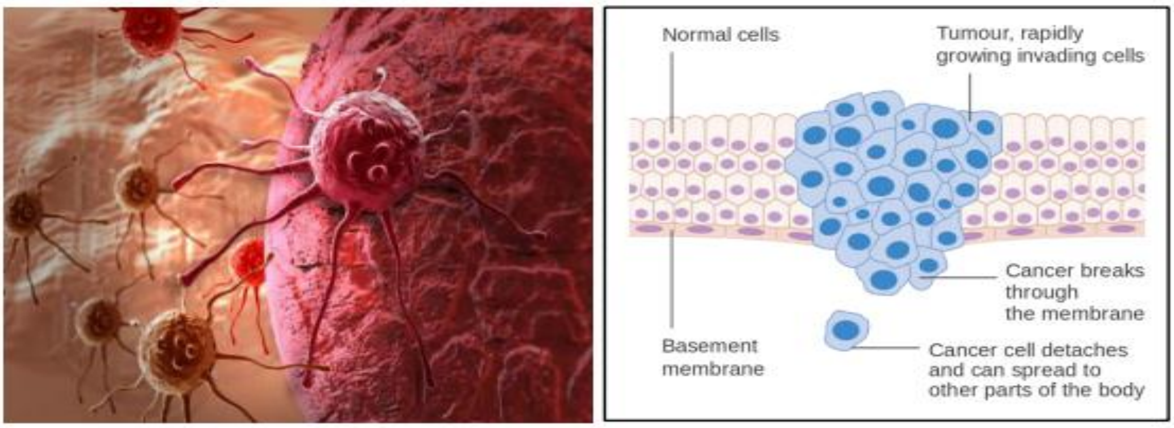

Fig. 3 Demonstration of Cancer Cells.

The skin is susceptible to numerous diseases, with skin cancer being a major concern.[21] Human skin is especially sensitive to various chemical mutagens and carcinogens that are encountered in everyday life.[22] Topical delivery of nutraceuticals is viewed as an effective and safe method for treating skin cancer.[23] In the modern era, the rise in UV radiation exposure, largely due to lifestyle changes, has contributed to an increase in the incidence of skin cancer.[24]

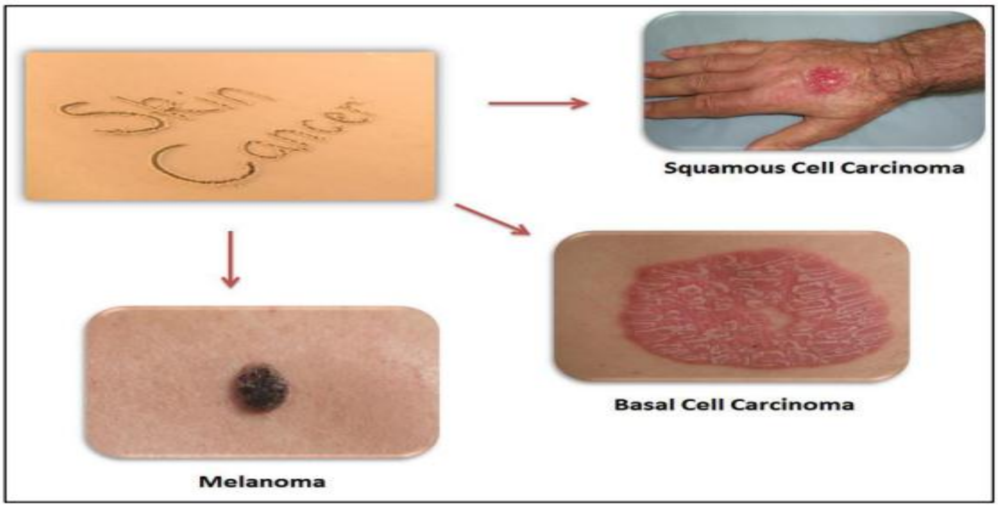

Fig. 4 Types of Skin Cancer.

Oncogenes play a role in regulating cellular communication with the external environment.[25] Topical chemotherapy is an appealing strategy due to its ease of application and non-invasive nature. However, delivering antineoplastic agents through the skin can be challenging because of their physicochemical properties, such as solubility, ionization, molecular weight, and melting point, as well as the barrier function of the stratum corneum. Various methods have been developed to enhance drug penetration, retention, and effectiveness.[26] Cancer treatment seeks to provide a path to cure this serious disease, allowing individuals to return to their daily lives.[27]

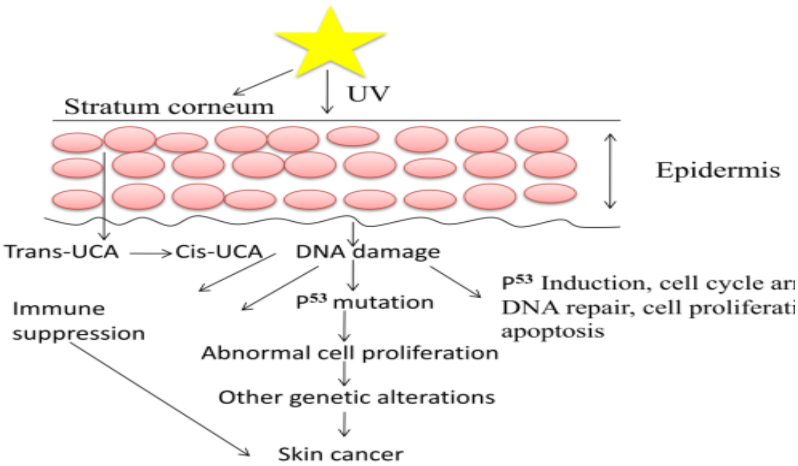

Fig. 5 Pathways involved in Skin Cancer Development.

THE ROLE OF AYURVEDA IN CANCER

Ayurveda, the ancient Indian system of medicine, has long been recognized for its use of plant-based drugs to prevent or manage various tumors. According to the Ayurvedic texts 'Charaka' and 'Sushruta Samhitas,' cancer is described as either inflammatory or non-inflammatory swelling, referred to as 'Granthi' (minor neoplasm) or 'Arbuda' (major neoplasm).[28] Although Ayurvedic treatment is highly effective, the mechanisms of action, pharmacology, pharmacokinetics, and pharmacovigilance of many key Ayurvedic drugs have not yet been fully explored.[29] Ayurveda promotes the body's self-healing abilities and offers a variety of therapies and herbs to purify and support bodily tissues for natural recovery. It can identify subtle disturbances at early stages of disease. Additionally, Ayurveda can help reduce treatment side effects and aid in the body's recovery process.[30] While modern medicine is evidence-based and relies on specific chemical entities for treatment, Ayurveda focuses primarily on disease prevention and the promotion of overall health through proper lifestyle choices and rejuvenation practices.[31]

The goal of Ayurvedic therapy in cancer treatment is to enhance the mind's self-healing abilities. Cancer and similar diseases impact not only physical health but also mental well-being. Disruptions between the mind and body can lead to various symptoms, including lethargy, anxiety, restlessness, and depression.[32] When cancer occurs, it disrupts the body and affects Tamas (the energy that maintains cohesion over time) and Kapha. Plants such as vinca, shattering, guduchi, triphala, and tulsi have been used as anticancer agents. Ayurveda aims to provide preventive, curative, therapeutic, and prophylactic care in cancer treatment. A primary focus of Ayurvedic cancer therapy is to balance and manage Tridosha (Vata, Pitta, and Kapha) and Triguna (Sattva, Rajas, and Tamas), which correspond to the fundamental elements of the universe and integral components of the mind.[33]

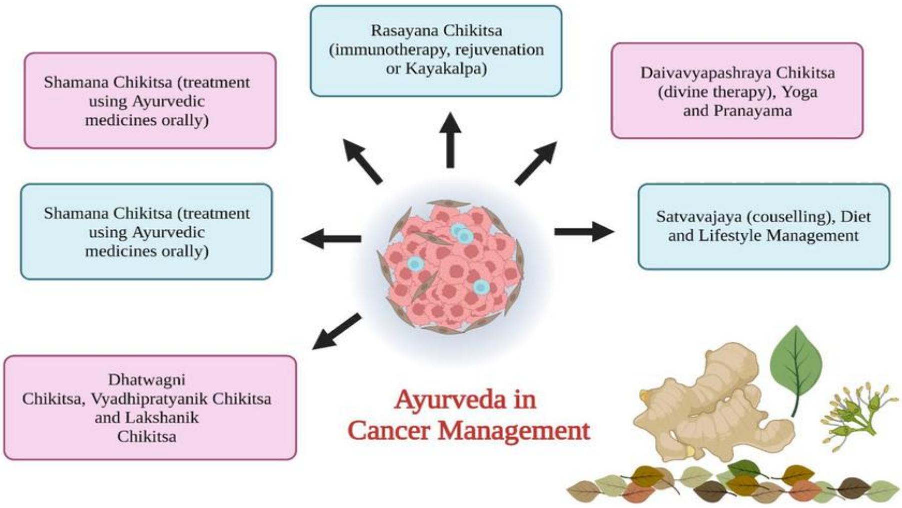

Fig. 6 Ayurveda in Cancer Management.

PHYTOCONSTITUENTS USED FOR MANAGEMENT OF SKIN CANCER

Many natural resources available worldwide hold potential for medical applications, yet many of them have not been fully explored for use in the pharmaceutical sector.[34] More than half of all medications available today have a natural origin, with over seventy percent of cancer treatments derived from such sources. These natural origins include plants, marine life, animals, and microorganisms.[35] In skin cancer, the outer layer of the skin becomes cancerous, which has traditionally been treated using herbal juices or extracts.[36]

Many developing countries continue to rely on natural medicines, often due to the high cost of synthetic drugs. According to the World Health Organization, about 80% of people in these countries depend on traditional medicinal practices to address and supplement their basic health needs.[37] The limitations of using natural products as medicines—such as stability, absorption, and therapeutic effects—can be addressed through Novel Drug Delivery Systems. These systems encompass various technologies, formulations, and approaches designed to deliver drugs effectively and safely, ensuring the desired therapeutic outcomes.[38] The use of herbal medicines has been on the rise due to their generally fewer side effects compared to synthetic alternatives.[39] The four major classes of clinically used plant-derived anticancer compounds are vinca alkaloids, taxane diterpenoids, camptothecin derivatives, and epipodophyllotoxin.[40]

Plants have served as a source of medicine for thousands of years, and phytochemicals remain vital in contemporary medical practices.[41] Ayurvedic formulations and the plants used in these preparations are gaining increasing attention worldwide.[42] Ayurvedic physicians conduct thorough analyses of host-drug interactions to prescribe personalized treatments for each patient.[43]

Today, certain natural compounds are recognized for their skin-protective effects.[44] Plant extracts with antioxidant properties have recently been utilized in topical applications to provide significant protection against UV-induced sunburn.[45] Plants and their extracts have been extensively used in the development of various therapeutic products and serve as valuable resources for drug discovery in the pharmaceutical industry.[46] Plants support individual health and vitality while also treating diseases, including cancer, without causing toxicity. Over 50% of all modern drugs in clinical use are derived from natural products, many of which have the capability to control cancer cells.[47] Herbs and spices are utilized to maintain and enhance human beauty due to their numerous beneficial properties, including sunscreen, anti-aging, moisturizing, antioxidant, anticellulite, and antimicrobial effects.[48]

Table 1. Natural medicine used as photoprotective for skin cancer.

Natural Photoprotective Agents	Source/Family	Components	Action/Uses
Tea	Green, black and oolong teas	Catechin, gallocatechin, gallic acid, kaempferol, myricintin	Potent antioxidant and can scavenge ROS
Curcumin	Root of Curcuma long Zingiberacea	Curcumin (diferuloylmethane)	Antioxidant, anti- inflammatory
Silymarin	Milk thistle (Silybum marianum)	Silybin, silibinin, silidianin, silychristin, isosylibin	Antioxidant and anticarcinogenic
Genistein	Soy, red clover, ginkgo biloba Greek oregano and Greek sage	Genistein	Antioxidant and anticarcinogenic
Garlic compounds	Allium sativum	Garlic sulphur compounds	Antioxidant and photochemopreventive
Apigenin	Vascular plants	4,5,7-Trihydroxyflavone	Anticarcinogenic
Anticarcinogenic	Grapes, nuts, fruits	Trans-3'4'5'-trihydroxystilbine	Potent antioxidant, anti-inflammatory and antiproliferative
Ginkgo biloba	Ginkgoacea	Quercetin, epicatechin rutin, apigenin	Antioxidant, anti- inflammatory and anticarcinogenic
Carotenoids	Green plants, carrots tomatoes etc.	B-carotene, lycopenes	Photoprotective
a- tocopherol	Plant oils	a- tocopherol	Photochemoprotective
L-ascorbic acid	Most fruits and vegetables	L-ascorbic acid	Antioxidant
Caffeic and ferulic acids	Vegetables, olives, olive oil	Caffeic and ferulic acids	Photochemoprotective

Herbal remedies were chosen as potential drug candidates for delivery through a nanodelivery system due to the following properties:

1. Effective extracts in chloroform, petrol, acetone, and methanol are available, but they may not be suitable for direct delivery.
2. These remedies are bulk drugs, allowing for potential dose reduction.
3. Currently marketed formulations often lack target specificity for various chronic diseases.
4. There are associated side effects with many existing formulations.
5. Patient non-compliance can result from large doses and limited effectiveness of available treatments.[49]

Curcumin (CUR) is a polyphenol derived from the rhizomes of turmeric, scientifically known as Curcuma longa Linn. (Zingiberaceae).[50] Curcumin (CCM), a naturally occurring polyphenol extracted from the turmeric plant, has garnered significant attention over the past few decades due to its diverse biological activities, including anticancer, antioxidant, anti-amyloid, anti-inflammatory, antidiabetic, antibiotic, and antiviral effects.[51] Curcumin is effective in preventing and alleviating gastric lesions.[52] Curcumin is the primary active component found in the rhizomes of Curcuma longa L.[53] Curcumin reduces melanin levels and inhibits tyrosinase activity in alpha-melanocyte stimulating hormone-stimulated B16F10 cells.[54]

Nanotechnology for Skin Cancer

Nanotechnology provides numerous advantages for medical applications, including early cancer detection and treatment, passive and active disease targeting, enhanced biocompatibility, and multifunctionality. This technology enables both imaging and therapeutic capabilities, allowing for simultaneous treatment and monitoring of diseases.[55]

A nanocarrier is a type of nanomaterial designed to deliver another substance, such as a medication. Common examples include micelles, polymeric systems, carbon-based materials, and liposomes.[56] The topical route for managing skin disorders provides several advantages over the oral route and holds significant potential for effective drug delivery.[57] Transdermal drug delivery using nanoparticles for skin cancers offers a promising alternative, as most chemotherapeutics are typically given systemically and can be toxic to healthy cells. This systemic approach often results in significant morbidity for cancer patients.[58]

Nanotechnology is viewed as a promising solution for delivering drugs precisely to target tissues, aiming to maximize therapeutic benefits while minimizing side effects.[59] Nanoparticles are typically defined as structures ranging in size from 1 to 100 nm, characterized by a high surface-to-volume ratio that imparts distinct properties compared to bulk particles of the same chemical composition. Due to their unique characteristics and small size, which allows them to penetrate cells and organelles, nanoparticles are utilized in a variety of biomedical applications both in vitro and in vivo.[60] This nanoscale range significantly alters the physical, chemical, and biological characteristics of materials, leading to unique phenomena and functions.[61]

1. Types of Nanoparticles used for Drug Delivery in Cancer Treatment

- Carbon magnetic nanoparticles
- Dendrimers
- Ceramic nanoparticles
- Chitosan nanoparticle
- Liposomes
- Low-density lipoprotein
- Nano- emulsion
- Micelles
- Nano spheres
- Nano vesicles
- Nano liposphere

2. Types of Herbal Nanoparticles used in Cancer Treatment

- Liposomal Drug Delivery Systems
- Phytosomal Drug Delivery Systems
- Microspheres Drug Delivery Systems
- Microemulsions systems
- Tranfersomal Drug Delivery Systems
- Ethosomal Drug Delivery Systems
- Solid-Lipid Nanoparticles systems (62)

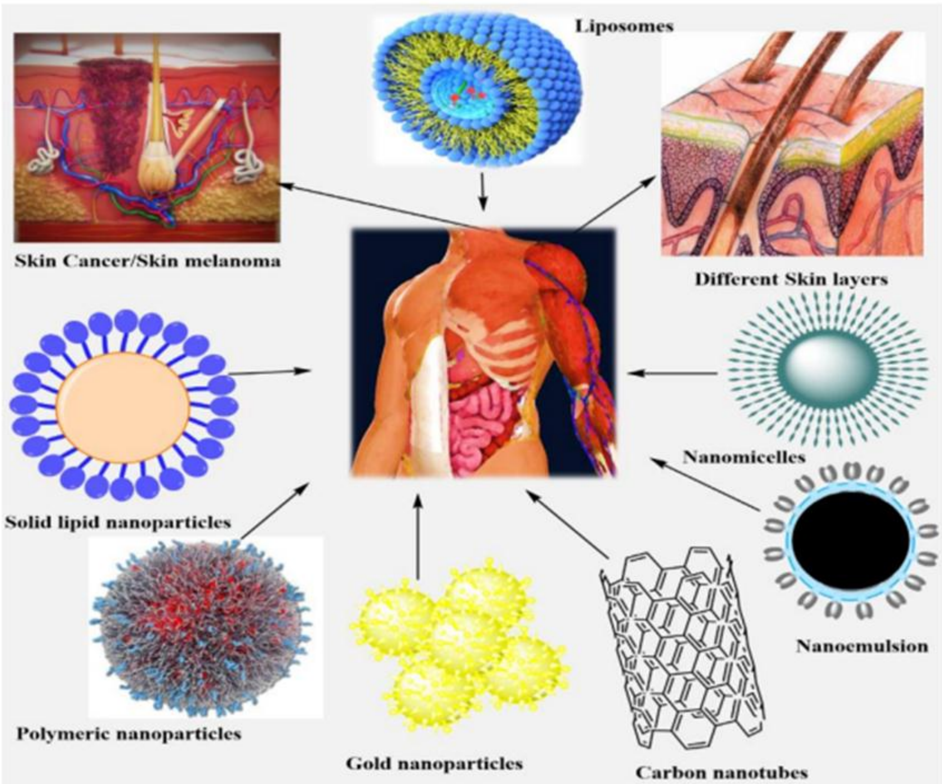

Fig. 8 Types of Nanoparticles.

Carbon magnetic nanoparticles

Carbon magnetic nanoparticles are small particles (ranging from 1 to 100 nm) composed of carbon materials combined with magnetic metals such as iron. These nanoparticles possess magnetic properties and find applications in drug delivery, MRI, and environmental remediation. In cancer therapy, they can target tumors directly for chemotherapy, reducing side effects and improving treatment effectiveness. Their biocompatibility and large surface area enhance their utility in various biomedical applications.[63]

Dendrimers

Dendrimers are nanoscale, branched polymers featuring a core and customizable surface properties. In cancer therapy, they are utilized to deliver drugs directly to tumors, which enhances treatment efficacy while minimizing side effects. Their distinctive structure also contributes to cancer diagnostics, making them valuable for both treatment and detection purposes.[64]

Ceramic nanoparticles
Ceramic nanoparticles are small inorganic particles (less than 100 nm) recognized for their stability and biocompatibility. In the treatment of skin cancer, they facilitate targeted drug delivery directly to tumors, improving therapeutic effectiveness while reducing damage to healthy tissue. Additionally, their properties support imaging, making them beneficial in both cancer diagnosis and treatment.[65]

Chitosan nanoparticles
Chitosan nanoparticles are biocompatible particles derived from chitosan, a natural polymer. They effectively encapsulate drugs for targeted delivery in cancer treatment, enhancing therapeutic efficacy while reducing side effects. Their biodegradability and nontoxicity make them promising candidates for both cancer therapy and diagnostics.[66]

Liposomes
Liposomes are spherical vesicles formed from phospholipid bilayers that can encapsulate drugs. In cancer treatment, they facilitate the direct delivery of chemotherapy to tumor cells, enhancing the effectiveness of the drugs while minimizing side effects. By improving the bioavailability of anticancer agents and enabling targeted therapy, liposomes are crucial in contemporary cancer treatments and drug delivery systems.[67]

Low-density lipoprotein (LDL)
Low-density lipoprotein (LDL) is responsible for transporting cholesterol in the bloodstream and is being investigated in cancer research for targeted drug delivery. Cancer cells typically exhibit an increased number of LDL receptors, enabling selective uptake of drugs loaded with LDL. This approach can enhance treatment effectiveness while reducing side effects.[68]

Nano-emulsions
Nano-emulsions are colloidal dispersions of oil and water stabilized by surfactants, with droplet sizes typically between 20 and 200 nm. They improve the solubility and bioavailability of hydrophobic drugs. In the treatment of skin cancer, nano-emulsions can deliver therapeutic agents directly to tumor sites, enhancing penetration and efficacy while minimizing systemic side effects. Their capacity to improve skin absorption makes them particularly valuable for topical applications in oncology.[69]

Micelles
Micelles are nano-sized aggregates created by amphiphilic molecules, featuring a hydrophilic outer shell and a hydrophobic core. In the treatment of skin cancer, they encapsulate hydrophobic drugs for targeted delivery to tumor cells, enhancing effectiveness and minimizing side effects. Their improved skin penetration also makes them suitable for topical applications.[70]

Nanospheres
(Nanospheres are spherical nanoparticles that range in size from 1 to 1000 nm and are composed of polymers or lipids. They are designed to encapsulate drugs for controlled release. In the treatment of skin cancer, they enable targeted delivery of chemotherapy directly to tumors, enhancing efficacy while minimizing side effects, making them effective for topical applications.[71]

Nano vesicles
Nanovesicles are small, spherical structures created by lipid bilayers, typically ranging from 50 to 1000 nm in size. They can encapsulate and deliver drugs, enhancing both solubility and stability. In skin cancer treatment, nanovesicles enable targeted delivery of therapeutic agents directly to tumor cells, improving treatment efficacy while reducing side effects. Their ability to penetrate the skin makes them especially useful for topical applications in oncology.[72]

Nanolipospheres
Nanolipospheres are small, lipid-based carriers that typically range in size from 100 to 1000 nm. They combine the characteristics of liposomes and solid lipid nanoparticles, providing enhanced stability and controlled release of encapsulated drugs. In skin cancer treatment, nanolipospheres effectively deliver chemotherapeutics directly to tumor cells, improving drug absorption and minimizing systemic side effects. Their capacity to penetrate the skin further enhances their utility in topical therapies. [73]

Liposomal drug delivery systems
Liposomal drug delivery systems utilize liposomes, which are spherical vesicles composed of phospholipid bilayers, to encapsulate drugs, thereby enhancing their stability and bioavailability. In cancer therapy, these systems target chemotherapy directly to tumors, reducing side effects and improving treatment effectiveness. Their versatility makes them suitable for a wide range of applications, both systemic and topical.[74]

Phytosomal drug delivery systems
Phytosomal drug delivery systems are nanocarriers that encapsulate phytochemicals within phospholipid complexes, enhancing their bioavailability and stability. In cancer treatment, these systems improve the absorption and targeting of therapeutic agents, increasing their efficacy and reducing side effects, while harnessing the advantages of natural compounds.[75]

Microsphere drug delivery systems
Microsphere drug delivery systems consist of small spherical particles, ranging from 1 to 1000 micrometers, designed to encapsulate drugs for controlled release. In cancer treatment, these systems target tumor sites and gradually release anticancer agents, improving treatment efficacy while reducing side effects. Their adaptability allows for multiple administration routes, including injectable and oral forms.[76]

Microemulsion

Microemulsion systems are stable, transparent mixtures of oil, water, and surfactants, with droplet sizes ranging from 10 to 100 nm. They enhance the solubility and bioavailability of hydrophobic drugs, making them effective for targeted delivery in cancer treatment. Additionally, their improved skin penetration makes them particularly useful for topical applications.[77]

Transfersomal drug delivery systems

Transfersomal drug delivery systems are flexible, nanometer-sized vesicles composed of phospholipids and surfactants. They enhance drug penetration through biological membranes, including the skin. In cancer treatment, transfersomes can effectively deliver therapeutic agents directly to tumor sites, improving drug absorption and efficacy while minimizing side effects. Their distinctive properties make them especially suitable for topical applications and transdermal delivery.[78]

Ethosomal drug delivery systems

Ethosomal drug delivery systems are lipid-based vesicles that incorporate ethanol to enhance skin permeability. These soft, flexible carriers improve the delivery of both hydrophilic and hydrophobic drugs. In cancer treatment, ethosomes effectively transport therapeutic agents directly through the skin to target tumors, increasing absorption and efficacy while reducing systemic side effects. Their unique formulation makes them especially valuable for transdermal applications in oncology.[79]

Solid-lipid nanoparticles (SLNs)

Solid-lipid nanoparticles (SLNs) are small lipid-based carriers made from solid lipids, typically ranging in size from 50 to 1000 nm. They provide controlled drug release and enhanced stability, making them suitable for encapsulating both hydrophilic and hydrophobic drugs. In cancer treatment, SLNs can deliver therapeutic agents directly to tumor sites, improving drug efficacy while minimizing side effects. Their biocompatibility and ability to protect sensitive drugs make them valuable for various delivery applications, including oral, parenteral, and topical routes.[80]

CONCLUSION

In the evolving landscape of skin cancer treatment, the fusion of nanotechnology with natural bioactive compounds emerges as a beacon of hope. This innovative approach not only addresses the limitations of traditional therapies such as systemic toxicity and poor specificity but also harnesses the therapeutic potential of nature's own arsenal. By enhancing the delivery mechanisms of phytochemicals through nanocarriers, we can achieve more targeted and effective treatment outcomes while minimizing adverse effects.

Moreover, the insights gleaned from Ayurvedic medicine underscore the value of holistic approaches in cancer therapy. As we continue to explore the synergy between modern science and traditional healing practices, we pave the way for more personalized and effective interventions. The journey ahead involves rigorous research and clinical validation to unlock the full potential of these novel delivery systems, ultimately transforming the standard of care for patients battling skin cancer. Embracing this integrative path not only fosters innovation but also reaffirms our commitment to improving patient lives through safer and more effective treatment strategies.

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