A Review in nanoparticles based treatment approaches for skin cancer

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing a degree at Brac University.

2. The thesis does not contain material previously

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3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.

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Approval

The thesis is titled –A review in nanoparticles based treatment approaches for skin cancer" submitted by Rahat Tasnim Tauna (ID: 18146046) of Spring 2022 has been accepted as satisfactory in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy.

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Abstract

Skin cancer has become the fifth most often reported malignancy worldwide, impacting both the financial and global health. The statistics on skin cancer have been further worsened by manufacturing, genetic modification, and the rapidly increasing environmental changes. Many problems with cost, toxicity, and bioavailability plague current treatment methods, including surgery, radiation, conventional chemotherapy, targeted therapy, and immunotherapy. As a result, patient compliance is low and anti-skin cancer therapeutic efficacy is declining. To date, there have been a number of nanotechnological developments that have helped to overcome this limitation. Of all the nanomaterials, nanoparticles have provided enormous benefits by serving as medication carriers and therapeutic agents for the amazing treatment of skin cancer. Through their poor blood vessels, the tiny size and great surface area to volume ratio of nanoparticles lead to increased treatment efficacy by increasing the absorption of skin tumors. In this regard, the current review offers up-to-date details on the various forms and pathophysiology of skin cancer, as well as the available treatments and side effects.The role of several lipid, polymer, and inorganic nanoparticles in the therapy of skin cancer is also thoroughly examined, and their patents and clinical trials are then reported.

Keywords: Skin cancer, melanoma, metal nanoparticles, nanotechnology, and polymers.

Dedication

Honoring my parents, who would stop at nothing to ensure my fulfillment of requirements.

Acknowledgement

I start by giving thanks to the Almighty Allah for providing me with the ability, power, and support I need to finish this endeavor, as well as for keeping me in good health. Still, without the assistance of many others, I could not have finished my research paper, and for that I am grateful.

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Table of Contents

List of Tables

List of Acronyms

NMsc - non melanoma

SC- skin cancer

Nps- nanoparticles

Uv- ultraviolet radiation

BCC- Basal cell carcinoma

SCC- Squamous cell carcinoma

PDT- Photodynamic therapy

MAL-methyl aminolevulinate

ALA- aminolevulinic acid

CTLA-4 cytotoxic T-lymphocyte antigen-4

EU-European Union

SLN- solid lipid nanoparticles

Dox- doxorubicin

PEG- polyethylene glycol

EPR (Enhanced Permeability and Retention)

CHAPTER ONE

1.1 Introduction

Skin cancer is the most prevalent form of malignant neoplasm among white people. Melanoma and non-melanoma skin cancer (NMSC) are becoming increasingly prevalent over the world. As a result, investigating and comprehending their present epidemiological tendencies is thought to be critical in order to achieve early and appropriate control of the diseases (Apalla et al., 2017) .Warning signs for the development of skin cancer include light complexions, genodermatoses, positive family histories, sun exposure, UV radiation exposure, and other factors. Since 2007, the annual cost of treating skin cancer has been predicted to be more than USD 8 billion.This is in contrast to the USD 3.6 billion in treatment costs from 2002 to 2006 (Diaz et al., 2023).

Considering nanotechnology can work with materials in the 1-1000 nm size range, it has attracted a lot of interest in a variety of medicinal applications, including cancer therapy. The distinct physicochemical characteristics of nanomaterial have the potential to significantly enhance the effectiveness of cancer treatments. NPs are a top choice for skin cancer therapy due to their multifunctional properties, which include acting as an anticancer agent, encapsulating and protecting therapeutic moieties, targeting tumors, overcoming chemoresistance, controlling drug release, and increasing skin permeability (Zeng et al., 2023).

Although their efficacy in treating dangerous tumors is well established, further research is necessary to fully understand their significance and promise in treating advanced cutaneous carcinomas.With a focus on significant NP categories and the benefits they provide for the advancement of cutaneous cancer therapies, we will examine and assess a collection of recent relevant studies in this section (Diaz et al., 2023).

1.2 Epidemiology

The early stage of skin cancer is more familiar among white people. The lifespan risk of progress at this early stage is about 0.1% of Black, 2.4% of Caucasian, and 0.5% of Hispanic people. Nonetheless, the standard age of diagnosis is about 60 and the risk of the stage is expanding with age. Throughout the last decade, the average epidemiologic data has been increasing constantly around Canada, Europe and the United States. In Australia and New Zealand, the percentage rate has increased over 40% and 50% over 100,000 persons in the year 2011 respectively. Subsequently in Europe and the US, the percentage rate has increased over 21.6% and 13.15% over 100,000 persons in the year 2012 respectively (Apalla et al., 2017). Based on the report ofUnited States Environmental Protection Agency, the consequence of acquiring skin cancer linked with a daily utilization of approximately 1.0 L of arsenic-polluted water at a concentration of 50 μg/L concentration has been estimated to be one to two in thousand. Arsenic pollution of groundwater in Bangladesh is said to be the worlds' one of the biggest issues in terms of impacted people. According to the survey from the 2010's, Bangladeshi people in general, mostly in rural areas, have been chronically exposed to arsenic through drinking water and daily meals is about 35 to 77 million (Choudhury et al., 2018).

1.3 Pathophysiology of skin cancer

Skin cancer is a syndrome where unusual cells grow and divide uncontrollably in the skin tissues or epidermis which is known as the outermost skin layer caused by unrepaired DNA damage. It causes mutations that cause skin cells to grow instantly and consequence in cancerous tumors. Moreover, persons who work outside or participate in sports are most likely to develop skin cancer. People with fair-skinned in particular have skin cancer because these kinds of people have less melanin. Melanin defines the protective pigment of the outer

layer of skin(epidermis), and helps to protect the skin from ultraviolet(UV) rays. Also,dark-skinned people and the people whose skin has not had significant sun exposure can develop skin cancer (Skin Cancer Information - SkinCancer.org, 2019)

1.3.1 Classifications of skin cancer

A significant stage that presents a variety of malignant skin malignancies is skin cancer. There are two primary categories of skin cancer.(Skin Cancer Information - SkinCancer.org, 2019) :

1) **Melanoma skin cancer (MSC):**

Melanoma is known as the most serious skin cancer because it spreads so huge to any organ. It causes a huge impact on life threatening conditions more like death . Melanoma comes from the skin cells called melanocytes. Melanocytes insure melanin, which gives our skin dark pigment color. Most melanomas are black and brown in color, but some of them are pink, red, purple or skin coloured (Melanoma - Skin Disorders, n.d.)&(Cleveland Clinic, 2019). In 2022, about 99,780 new cases of melanoma are estimated to occur in the United States, causing an estimated 7,650 deaths (Melanoma - Skin Disorders, n.d.).Although it occurs less than 5% of all skin cancers diagnosed in the United state. It produces symptoms like a changed mole in terms of size, shape, and color, as well as irregular borders, itching, and bleeding on occasion. Tanning beds with ultraviolet A (UVA), sun exposure, and family members with melanoma increases the risk of melanoma. To prevent melanoma avoiding the sun, using sunscreen and wearing protective clothing like covered dress up can be helpful. Treatment like removal of the tumors and taking cryotherapy, radiation therapy are kind of beneficial. Doctors treat melanomas by cutting them out which is known as Mohs microscopically controlled surgery(Melanoma - Skin Disorders, n.d.).

2) **Nonmelanoma skin cancer (NMSC) or Keratinocyte cancer:**

Despite being significantly more frequent than melanoma, the majority of NMSCs have far better prognoses and are far more curable. The two primary kinds are keratinocytes on the epidermis, which generate basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Compared to melanoma, they are substantially less lethal and much easier to cure because they are still restricted to site infection. (Melanoma - Skin Disorders, n.d.).

- **Basal cell carcinoma (BCC) :** Rarely, basal cell carcinomas (BCCs) develop out of control from the skin's basal cells in the epidermis, the outermost layer of skin. In the US, 3.6 million cases are diagnosed annually (Melanoma - Skin Disorders, n.d.). Fair-skinned individuals are more likely than dark-skinned individuals to experience this. The consequences of basal cell carcinoma spreading are severe, dangerous, and sometimes fatal when it develops close to the mouth, eyes, bones, or brain. In this situation the tumor's growth is slower which is almost not noticeable . There are variations of basal cell carcinoma like nodular, superficial spreading, sclerosis (morpheaform) and pigmentation. Basal cell carcinoma causes lumps that may be itchy or painful, lumps may grow slowly over time. Basal cell carcinoma is available in our face, scalp, nose, eyelids, ears, arms and legs.(American Academy of Dermatology Association, n.d.) To prevent this firstly, we need to avoid sun exposure from 10 am to 4 pm. Secondly, taking vitamins B3 twice a day can reduce the risk of developing BCC and SCC. Finally, wearing clothes that have built-in sun protection (UPF). Vismodegib and Sonidegib drugs are used along with some side effects under doctors recommendations. Treatment like surgery, cryotherapy, chemotherapy , laser therapy, photodynamic therapy etc can be beneficial (Melanoma - Skin Disorders, n.d.).
- **Squamous cell carcinoma (SCC):** SCC is the second most common type of skin cancer which begins in the squamous cells in the skin. Every year in the United

States, 1.8 million people are diagnosed with squamous cell carcinoma and 15,000 deaths cause it (Melanoma - Skin Disorders, n.d.). SCC damage includes precancerous skin growth caused by previous sun exposure, in mouth precancerous growth as white or red spot (leukoplakia or erythroplakia). Bowen disease and possibly keratoacanthomas are forms of SCC. In our skin,mouth,tongue,stomach(epidermoid carcinoma),anal cavity we can find SCC(American Academy of Dermatology Association, n.d.). To prevent SCC we need to avoid the sun, using sunscreen and wearing protective clothing like a covered dress up can be helpful.Proper identification and treatment can slow the rapid growth of SCC and stop it from spreading to other body areas. Treatment like surgery, cryotherapy, chemotherapy , laser therapy, photodynamic therapy etc can be beneficial (Melanoma - Skin Disorders, n.d.).

1.3.2 Rare skin cancer and variations

There are some other types of skin cancer which are rare but show a deadliest effect on the affected people. They are:

- Merkel cell carcinoma
- Sebaceous carcinoma
- Dermatofibrosarcoma protuberans(DFSP)
- Atypical fibroxanthoma
- Cancer of skin glands
- Kaposi carcinoma etc.(Cleveland Clinic, 2019)

Most of the skin cancers are curable when specially treated at their initial phase. But when in the primary stages if they are not getting properly treated,skin cancer spreads huge in different parts and organs of our body which causes the deadliest to get recovered.(Cleveland Clinic, 2019)

1.3.3 Risk factors

Tanning, Sunburn, UV radiation, Atypical mole, Photosensitivity and depending on the skin type mainly are the risk factors for skin cancer. Also,

- Spending a considerable amount of time under the sunlight or in a sunny climate.
- Getting easily sunburned or having a lack of melanin.
- Tan or use tanning beds.
- Have many moles or unusual-shaped moles.
- Having a family history of skin cancer.
- Due to an organ transplant.
- Have acting keratosis and freckled skin.
- Taking medication which causes weakness of the immune system(Cleveland Clinic, 2019)

1.3.4 Recent treatment approaches and their limitations

Skin cancer can be treated and recovered using belongings therapies. They are:

1) **Mohs micrographic surgery:** SCC and BCC the two most common skin cancers are recoverable by the technique known as Mohs Surgery. It allows to recure all the cancerous cells by sparing healthy tissues and removal of tiny scars. Previously the technique was named as chemosurgery. In the mid 1960s, the procedure of the technique was recognized as it had a vast potential in the field of dermatology by Dr. Mohs (Skin Cancer Information - SkinCancer.org, 2019). The technique is followed by some procedures and stages like examination and preparation,top layer removal, lab analysis, microscopic examination , second layer removal, wound repair , finishing up. It helps to recover unnecessary harmness to usual tissues. It is an

efficient and cost effective treatment for local anesthesia. This technique confirms 94% skin cancer prevention after treatment(Cleveland Clinic, 2019).

2) **Cryotherapy:** To destroy the rare tissues we need to apply extreme cold to freeze using liquid nitrogen or argon gas the technique is known cryotherapy. This technique is also named as cryoablation. It causes no complications of bleeding and recurrence with high rate of tumor prevention(Cleveland Clinic, 2019). The limitations of this technique is marginal evaluations are not achievable because it is considered a skilled professionals dependent procedure. This technique is less effective for skin cancers. It also has complications like bone fracture, nerve damage, cramping or pain after cryotherapy (Zeng et al., 2023).
3) **Radiotherapy or Radiation therapy:** To kill cancer cells, usually high-powered X-rays are used in the technique known as radiation therapy. Radiotherapy is classified into 2 categories: external beam radiation therapy and internal radiation therapy. This therapy stops multiplying cancer cells and tumor cells. The side effects are nausea, vomiting, skin irritation, fatigue, abdominal bloating etc. Volumetric area therapy, a moderate radiation approach, is used to distribute medicine dosages appropriately in normal tissues. Radiation therapy has a number of drawbacks, the most significant of which are its high treatment costs and many session requirements(Cleveland Clinic, 2019).
4) **Photodynamic Therapy (PDT):** First, a photosensitizing component of methyl aminolevulinate (MAL) or aminolevulinic acid (ALA) is applied topically to the skin. PDT has far more therapeutic and cosmetic advantages than excisional procedures for skin cancer. Hematoporphyrin ether, the active ingredient, absorbs light to generate singlet oxygen and hazardous characteristics. Sadly, the medication gets activated and starts to eradicate skin cancer while slightly damaging healthy tissues when the skin

undergoes exposure to a concentrated laser beam. Since deep tissues cannot be accessed, the procedure is an expensive kind of treatment(Zeng et al., 2023).

5) **Immunotherapy:** Using the patient's immune system to attack cancer is known as immunotherapy. The best treatment for prolonging a patient's life with skin cancer is immunotherapy. It aids in the destruction of cancer cells by enhancing the immune system. Immunotherapy includes immune system modulators,cancer vaccines, monoclonal antibodies, adoptive cell treatment (T-cell transfer therapy), and checkpoint inhibitors. Checkpoints help to protect the damaging cells from overreacting. It connects with protein on the surface of T-cells. It works against the cytotoxic T-lymphocyte antigen-4 (CTLA-4) as an immunoglobulin. Treatment for larger BCC lesions appears to be less effective because the deeper component of the tumor is hidden by the focus on the surface area of the tumor(Cleveland Clinic, 2019).
6) **Chemotherapy**: Chemotherapy is given the benefit of the entire. This suggests that it goes through the bloodstream and throughout the body. Since chemotherapy spreads throughout the body, it may cause damage to normal tissue as it goes through its normal cell cycle. Chemotherapy can therefore have unfavorable side effects such nausea and hair loss. Chemotherapy is useful in preventing and treating a variety of superficial lesions, such as BCC and SCC in situ. Furthermore, those from lower and medium class backgrounds can afford chemotherapy. PTX must be generated in order to target cancerous cells and stay away from healthy cells to minimize cytotoxicity and adverse effects. In this regard, drug delivery systems based on nanoparticles offer a viable alternative for delivering anticancer medications for the treatment of skin cancer as well as for diagnosis (Cleveland Clinic, 2019).

1.4 Nanoparticles and Nanotechnology

According to the European Union (EU) commission nanoparticles are substances with dimensions smaller than 100 nm which have numerous appearances like spheres, rods, dendritic shapes etc (Raszewska-Famielec & Flieger, 2022). Nanoparticles subclasses like metallic nanoparticles (including metal oxides), gold shell nanoparticles particles , nanofibers (including the carbon nanotubes), fullerenes and quantum dots play an important role in human skin. Nanospheres and solid lipid nanoparticles (SLN) are extensively utilized in drug delivery related to skin cancer diseases and have been implemented in cosmetics and pharmaceutical products. While TiO2 & ZnO are mostly formulated in sunscreen formulations that can protect our skin against UV rays (Smijs & Bouwstra, 2010). Moreover, drug delivery has the potential to improve drug absorption, provide customized skin release with increased therapeutic efficacy, and reduce the need for several drugs.The capacity of nanoparticles to easily pass through cell membranes and biological barriers is a crucial feature in the medical area, which includes dermatology and dermocosmetology(Niska et al., 2018). When it comes to skin-related conditions, nanoparticles are especially helpful because they promote chemical changes and reduce unnecessary damage. When compared to traditional therapy, drug delivery using nanoparticles proved to be much more beneficial for patients with skin cancer. Through surface modification, nanoparticles can penetrate the skin and transport medications to specific tumor locations.Many studies have been conducted in an effort to identify new and better nanoparticles that may be effective in delivering drugs to treat skin conditions.Aside from the clear benefits of employing nanoparticles for cancer therapy, the majority of therapies based on nanotechnology are still in the early phases of development. Nonetheless, a few nanoformulations are now on the market and have already advanced through clinical studies to treat certain cancers. Doxil® (Janssen Biotech, Horsham, PA, USA) is a doxorubicin (Dox) formulation that is used to treat multiple myeloma, ovarian,

and breast cancer, as well as liposomes containing polyethylene glycol (PEG) (M. Zhao et al., 2017). Comparing Doxil® to free Dox, there is a seven-fold decrease in cardiac cytotoxicity and a hundred-fold longer blood half-life (Gabizon et al., 1994).

The use of nanotechnology in the diagnosis and treatment of cutaneous diseases as well as the preservation of healthy skin is growing. Subatomic interactions with epidermal tissue form the basis of nanotechnology (Gupta et al., 2013). By extending the stability of active compounds on the skin, one can alter drug penetration and permeation (Hadgraft, 2001), make direct contact with the stratum corneum and skin appendages (Guterres et al., 2007), and protect the drug against physical or chemical degradation. NPs offer significantly more cost-effective, precise, and successful therapy options (Gupta et al., 2013).

1.4.1 Nanotechnology in skin cancer treatment

Because of package protection, drugs delivered by nps may have had a longer biological half-life. Along with the EPR (Enhanced Permeability and Retention) consequence, they may be more intense at the cancer site (Prabhakar et al., 2013). EPR is influenced by the tumor vasculature's leakiness and insufficient lymphatic drainage (Gabizon et al., 1994). Nanotechnology therefore maximizes therapeutic potential while lowering side effects. Second, pharmacological treatments are based on the reality that nanoparticles can represent multiple medications. It is well recognized that immunotherapy leads to noticeably better treatment outcomes when combined with chemotherapy or targeted therapy (Bei et al., 2010). Thirdly, due to their stealth-like characteristics, nanoparticles can secure drugs made of sensitive proteins or siRNA (small interfering RNA) from the body's biochemical breakdown (Moghimi & Hunter, 2001). Consequently, the drugs stored in nanoparticles have been continuously distributed. Furthermore, nanoparticles can be structured to carry out a variety of functions, including image contrast and cancer cell targeting (Prabhu & Patravale, 2012).

Many nanoparticles have been investigated for the treatment of melanoma, including liposomes, polymersomes, dendrimers, inorganic nanoparticles, and carbon and protein based nanoparticles. Dermatologic pills guard the skin from the service disruptions in plasma levels carried on by the systemic administration of therapeutic ingredients that quickly carry off. (Prabhu & Patravale, 2012).

1.4.1.1 Varieties of nanoparticles approach for skin cancer

Nanoparticles are mainly classified into 2 types:

Organic nanoparticles (polymer based and lipid based) & Inorganic nanoparticles (Diaz et al., 2023).

1. Organic nanoparticles: In comparison to inorganic nanoparticles,organic nanoparticles have shown more effectiveness regarding cancer-targeting ligands and their ability in different medications associated with organic nanoparticles. Organic nanoparticles are utilized in mostly liposomes, solid lipid nanoparticles, polymeric nanoparticles, dendrimers, mAb nanoparticles in the study of skin cancer medications (Diaz et al., 2023).Various kinds of organic nanoparticles which plays an essential part in the skin cancer treatment are describing below:

- **Polymer based nanoparticles:**

Specialized drug carriers called polymer-based nanoparticles (NPs) are created from naturally occurring or manufactured polymers and span in size from 10 to 1000 nm. These can conjugate, adsorb, entrap, or encapsulate anticancer drugs for controlled release, tumor targeting, protection, and improved tumor absorption. They are categorized into nanocapsules and nanospheres. These NPs' easy synthesis, biocompatibility, biodegradability, and affordability have made them promising for use in the development of anticancer medicines loaded with polymer-based NPs to treat skin cancer situations. Several NP kinds and how they're used in skin cancer treatment in the future which are subclasses of polymer-based

nanoparticles such as polymeric nanoparticles, polymeric micelle, dendrimer, polymersome etc are playing an important role in anticancer related drug formulation for the skin cancer medications (Zeng et al., 2023).

- **Lipid-based nanoparticles:**

Lipid-based NPs are distinct carrier systems consisting of either lipid bilayers (ethosomes, liposomes, niosomes, etc.) or solid lipid nanoparticles and lipid carriers containing nanoparticles. In addition to liquid lipids, there are also aqueous cores (nanostructured lipid carriers) and solid lipid cores (solid lipid nanoparticles). Liposomes, ethosomes, niosomes, and so forth Either dissolved or disseminated, the therapeutic components are distributed through several pathways.The hydrophilic anticancer substances found in nature struggles with permeability and hydrophobicity.Insufficient aqueous solubility of anticancer moieties poor therapeutic efficacy . Moreover, chemotherapy drugs often have the potential to eliminate all cells, healthy and malignant, when they are free to enter the body's circulatory system. However, particular anticancer drugs are susceptible to deterioration in either environmental factors, such as light, temperature, or humidity, turning off their healing characteristics. All of these drawbacks may be overcome, and the lipid-based NPs are shown to be the most effective.Lipid-based nanoparticles (NPs) are the most extensive class of nanomedicines that the FDA has authorized to date due to their better safety profile. Skin cancer has shown remarkable response to the use of solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, niosomes, transfersomes, ethosomes, and other lipid-based NPs, many of which will be discussed in depth in the sections that follow. (Zeng et al., 2023).

- **Solid-lipid nanoparticles:**

SLNs, or colloidal lipid carriers, were originally made accessible in 1991. They typically range in size from 50 to 1000 nm.They originated from natural lipids that are solid at

physiological and ambient temperatures, such as fatty acids, steroids, waxes, monoglycerides, diglycerides, and triglycerides. As the name suggests, the solid lipid that makes up the core lipid matrix of SLNs ranges from 0.1-30% w/w and, depending on how it was created, can encapsulate either lipophilic or hydrophilic drugs. Surfactants (0.5–5% w/w) are then added to regulate the lipid matrix core.However, they are presently the most competitive drug carriers for skin cancer therapy due to their capability to encapsulate anticancer medicines and securely transport them to the tumor site to accomplish controlled release without engaging any permeability or toxicity difficulties.An in vivo pharmacokinetics analysis demonstrated that DHA-dFdC@SLNs had the greatest oral bioavailability when compared to free DHA-dFdC. Further support for this was given by the melanoma-bearing mice model, which showed that oral DHA-dFdC@SLNs had a higher maximum survival rate than free DHA-dFdC. In a second trial, Kim and colleagues tried to establish sustained administration of DTX for 24 hours after delivering it orally by encasing it in SLNs, which would lessen the toxicity of intravenous DTX. (Zeng et al., 2023).

2. Inorganic nanoparticles: As therapeutic drug delivery systems for skin cancer prevention (also known as from sun protection) and treatment, inorganic nanoparticles like titanium dioxide, zinc oxide, carbon nanotubes, gold, silver, and silica have undergone extensive testing(Diaz et al., 2023). Inorganic nanoparticles (NPs) have garnered a lot of interest due to their several applications in oncology, which include tumor therapy, tumor drug delivery, tumor imaging, and augmentation of radiation therapy. Metals, metal oxides, carbon, silica, ceramics, and other materials can be found in these nanoparticles (NPs). Skin cancer treatment is best served by inorganic nanoparticles (NPs) because of their unique physicochemical properties, including substantial surface area, bioactivity, biocompatibility, and functionalizing capacity at a small size. Researchers have discovered that inorganic NPs have an inherent therapeutic capability that allows them to kill cancer cells on their

own.However, they can also function as photosensitizing or photothermal agents, which are then used in photodynamic or photothermal therapy (PTT/PDT), respectively. Inorganic nanoparticles (NPs) possess unique synergistic features that can effectively treat skin cancer.These include the ability to transport drugs, their inherent medicinal qualities, and their photothermal or photosensitizing effects. (Zeng et al., 2023).

- **Gold nanoparticles (AuNPs)**

Since AuNPs can be conjugated to other molecules and have highly biocompatible surface properties, they have been demonstrated to accumulate and penetrate tumoral tissue productively. AuNPs are beneficial for photothermal therapy (PTT) because they efficiently absorb photon energy after laser exposure and transform it into heat, which can dissolve and cause impacts on natural cancer cells. PTT studies employing AuNPs have repeatedly demonstrated extended survival in models of melanoma tumors, as well as efficient tumor regression as a result of skin cancer cells dying off, with little harm to the surrounding healthy tissue.Moreover, AuNPs have demonstrated effectiveness in promoting cellular uptake, which raises the cost of apoptosis and reactive oxygen formation in skin cancer cells, and sustaining photosensitizers in biomedical applications . By conjugating AuNPs to other molecules or coating them with other materials, their features have been optimized. The rapid physiological clearance of NPs by the monocyte–macrophage system has been drastically decreased by coating AuNPs with materials such as red blood cell membranes. Improved cellular uptake and increased PTT effects have been made possible by the conjugation to cell-penetrating peptides, such as the tumor-targeting adaptor folic acid.

Because AuNPs can selectively enter tumor cells and stop the growth of cancer cells, using them in conjunction with other anti-skin cancer therapies has shown efficacy. It might be helpful to analyze the implementation of AuNPs with alternative drugs in more depth (Diaz et al., 2023).

- **Silver nanoparticles (AgNPs)**

Manufactured Ag NPs coupled with synthesized Ag NPs (microbial) and utilized the bacterial strain Bacilluslicheniformis as a catalyst for photodynamic treatment (PDT) on cell lines of cutaneous melanoma (B16F10) and epidermoid carcinoma (A431).Using polyethylene glycol (PEG) on cell lines (B16F10 and A431), the cytotoxicity of pure NPs and NPs coupled with 5-aminolevulinic acid was assessed and compared to the 5-aminolevulinic acid standard. The goal of this work is to create AgNPs on carboxylate nanocrystal cellulose (cCNC) using a hydrothermal process in order to minimize the amount of chemical reagents needed and provide a constant anchor for the controlled release of Ag +. Ag-carboxylate nanocrystal cellulose has been rapidly and efficiently metabolized using ammonium persulfate (APS) oxidized cellulose and a two-stage hydrothermal reaction. This has resulted in a significant reduction in the requirement for chemical reagents, such as Ag nitrate for the hydrothermal reaction and lowering or stabilizing ammonium persulfate for surface-modified cellulose. (Marzi et al., 2022). AgNPs create free radicals that damage cancer cells' DNA and mitochondria, disturbing the homeostatic balance within the cell. The formulations employ only brand-new, inexpensive, all-natural ingredients that work together to target nonmelanoma skin carcinoma (NMSC) with the least likelihood of drug resistance and cancer relapse. The epidermoid A431 skin cancer cells undertake a structural and cellular metamorphosis that was assisted by a similar combination of AgNPs and sericin. The in vivo outcomes demonstrated how T cell-mediated defense activated immunoglobulin (IgM) secretion. Lastly, this research proposes a novel strategy for the therapy of NMSC by applying biocompatible formulae made available through ethosomes (Marzi et al., 2022).

- **Mesoporous silica/ Silica nanoparticles (SiNPs)**

SiNPs, or silica core polyethylene glycol shell NPs, are able to work as drug delivery molecules and get beyond the toxicities that many anti-skin cancer medicines pose, which limit the dosage. They are an effective supplemental medication for the treatment of skin cancer since they are eliminated by the kidneys and have poor tissue absorption in the majority of organs. Since SiNPs have good pharmacokinetics and minimal tissue accumulation, cell-targeting compounds have been added to them to better target cancer cells. The emergence of lung micrometastases was almost completely eliminated by SiNPs loaded with verteporfin, and a mouse model of melanoma displayed less lymphangiogenesis. Research conducted both in vitro and in vivo has shown that SiNPs loaded with cisplatin effectively limit tumor growth, and they also showed less harm in healthy cells when compared to cisplatin therapy alone. Two melanoma cancer lines' cells were effectively cytotoxic when revealed to resveratrol-loaded SiNPs since resveratrol's bioactivity and dissolution rate were advanced.All things considered, SiNPs have advantageous pharmacological properties that can be used in conjunction with other treatments to increase their effectiveness and raise results (Diaz et al., 2023).

- Carbon nanotubes

  Rolling graphene sheets form cylindrical nanostructured carriers known as carbon nanotubes (CNTs).Because of their unique structural, mechanical, electrical, and thermal characteristics (PTT), CNTs are a good fit for cancer treatment. Due to their large surface area, carbon nanotubes (CNTs) can be used to adsorb or utilize disulfides as linkers to load high quantities of anticancer medicines. Furthermore, stimuli-responsive materials may be added to CNTs to create controlled medication delivery**.** (Zeng et al., 2023). Research has also looked into the possibility of using CNTs' skin permeability to apply medicinal medicines transdermally. However, it has been discovered that CNTs by themselves are unable to penetrate skin. Fewer

investigations, however, have documented the enhanced skin permeability of CNTs after iontophoresis and lipid/polymer functionalization. These and other evidence encourage biologists to investigate their possible use in the treatment of skin cancer.As a result, this nanosystem may find useful utilizes in the treatment of melanoma, particularly in the targeted delivery of strong hydrophobic anticancer medications to the tumor tissues.Because of their high photothermal conversion performance and ability to absorb NIR, CNTs are attractive options for PTT. Nevertheless, the free CNTs injected intravenously are not able to target tumors (Zeng et al., 2023).

1.5 Aim of the project

The focus of this review is on the possible future applications of nanoparticles (NPs) in the treatment of skin cancer, along with the challenges associated with their development.. With an eye toward NPs' potential future use in the field of skin cancer treatment, the various NP types now being investigated for diagnostic and therapeutic purposes have been discussed.

CHAPTER TWO

Methodology

The review process involved the selection, analysis, and summarization of pertinent literature. This review's data and information were gathered from pertinent publications. An electronic search has been conducted to compile the journals related to this subject. An outline was made to convey the data in accordance with the project objectives after carefully examining the data from a few recent articles. The goal of the study indicated that it was crucial to investigate skin cancer therapy strategies based on nanoparticles, as well as their mechanism of action and important implications. A comprehensive search was conducted through official websites and research databases to obtain as much crucial information as possible about the use of nanoparticles to treat skin cancer. This included a review of many journals, research papers, and review articles. The following pertinent literature was gathered, along with pertinent and significant keywords: polymer, solid lipid nanoparticles, liposomes, nanostructured lipid carriers, niosomes, ethosomes, skin cancer, metal nanoparticles, and nanotechnology. A few papers dealt with the topic of skin cancer treatment and nanoparticle technology. The title and keyword content of 55 articles have been evaluated. Once the abstracts were read, the number of papers was limited to twenty. This review article consisted of 35 selected papers that were read in their entirety. Mendeley software was utilized to ensure fair and correct reference, honoring the author's original works.

CHAPTER THREE

Result

3.1Table of Several types of nanoparticles proven for clinical trials : (Marzi et al., 2022)

Table1: Several types of nanoparticles proven for clinical trials.

Types of the nanoparticles	Cells	Results	Year
Silver nanoparticles	B16F10 and A431 cell lines	The greatest ROS generation in 5-ALA silver nanoparticle conjugates was seen in irradiated cells, showing drug activation in both B16F10 and A431 cells.	2019
	Human malignant melanoma (A375 cell line, ATCC number CRL-1619)	Regarding human skin, the nanoparticles have demonstrated strong anticancer action cancerous cells	2021
Gold nanoparticles	Murine B16 melanoma cells	Siberian ginseng gold NPs had a very low CC50 dosage against B16 murine melanoma cells.	2019
Magnetic nanoparticles	B16-F10 murine melanoma cells	Important immunological and cytotoxic gene expression is increased by magnetic nanoparticles, hypothermia, and	2020

		low-dose radiation on their own, and is amplified in combination treatment.	
Iron oxide nanoparticles	Murine B16 melanoma cells	Salicylic acid-functionalized iron oxide nanoparticles (NPs) showed promise as a treatment for B16F10 melanoma, since the iron oxide core exhibited cytotoxic properties and the salicylic acid coating had antiangiogenic and chemotherapeutic properties.	2020
Zinc oxide nanoparticles	Murine B16 melanoma cells	shown notable inhibitory action on the expansion of cancer cells	2021
Titanium dioxide (TiO2) nanoparticles	F10 melanoma mouse cell line	In melanoma mice, TiO2 nanoparticles are neither cytotoxic nor metastatic; when combined with cisplatin, they can enhance the therapeutic response by up to 50% and further suppress tumor development than when used alone.	2021

3.2 Investigations on different types of lipid based nanoparticles

Table no 2 : Latest investigation on different types of lipid based nanoparticles based therapeutic approaches for skin cancer:(Marzi et al., 2022)

Type	Therapeutic agent	Particle size	In vitro cytotoxicity study	Route of administration
Solid lipid nanoparticles	Doxorubicin	92 ± 2 nm	Mice melanoma cell line (B16F10)	Topical
Liposome	Dipalmitoyl phosphatidyl Choline, Cholesterol	207 ± 20 nm		Melanoma-bearing male C57BL/6 mice
Nanostructured lipid carriers	Lipid Sefsol, Geleol		Mice melanoma cell line (B16F10)	Melanoma-bearing albino Swiss mice
Niosomes	Span 60, Tween 60	125.34 ±13.29 nm	Human melanoma cell line (A375)	

Ethosomes	Ethanol, Phospholipon 90 G, Cholesterol	559.77–562.90 nm		Basal cell carcinoma bearing male Swiss albino mice

CHAPTER FOUR

Discussion

Following a specified technique from the National Institute of Health (NIH), a complete study of the antiproliferative and anticancer effects of AgNPs in melanoma under standard circumstances was carried out. There was polyvinylpyrrolidone (PVP) coating these NPs. Table No. 1 shows that the average size of the NPs was 35 ± 15 nm, with an Ag-metal concentration of 1.2%. Significant alterations in cell longevity, induction of death and apoptosis, and generation of reactive oxygen species were seen in B16-F10 cells following six hours of exposure to Ag particles or cisplatin.The doses of 3, 6, and 12 mg/kg AgNPs gave a survival rate that was roughly 4 times larger than cisplatin, according to in vivo experiments. Additionally, the genetically damaging effect determined by counting the number of micronuclei in the surrounding blood cells was not displayed by the living mice given AgNPs. AgNPs are incorporated into carboxymethylcellulose (CMC) polymer matrices, which are then coupled with citric acid and doxorubicin (DOX).These hybrids were created for use in nanomedicine to treat skin cancer via an all-green chemical approach. CMC polymers were used to create results that show a neutral AgNPs formulation has a strong anticancer impact and mark the first step in treating melanoma with these AgNPs, which can greatly reduce the adverse effects of present chemotherapies (Marzi et al., 2022).

A unique dual-purpose hybrid hydrogel with antimicrobial action that is intended to be used against skin cancer cells. te supramolecular tiny structures (in situ chemical reduction of Ag+ by a single-pot) (Capanema et al., 2019).

Using an aqueous extract of Siberian ginseng, a potent and economical biocompatible gold/AuNP was created. The synthesized AuNP matched every characteristic of a powerful AuNP, based on the physicochemical properties. The produced AuNPs' spherical form, size, and crystalline material were all indicated by the findings, which showed a surface plasmon resonance peak at 538 nm that remained stable for 30 days of incubation. These results

demonstrated that the biological components of Siberian ginseng produce NPs and decrease gold ions. Following discovery, melanoma cells from B16 mice were used to test the Siberian ginseng-AuNPs' anti-melanoma properties in vitro.The potential of the mitochondrial membrane was decreased and ROS levels were raised by SG-GNPs.Consequently, using SG-GNPS (which resembles trihydride boron (BH3)) increased the rate of proapoptotic proteins and decreased the antiapoptotic proteins in melanoma cells (Marzi et al., 2022).

After pelting melanoma cells with MNPs, they were exposed to an alternating magnetic field (AMF) in order to achieve the required thermal dosage of 2.5 μg Fe/106 cells.The HSP70 gene, which tolerates heat and inflammation, as well as other receptor gene pathways connected to adsorbent chemistry and toll-like receptors, greatly elevated in response to the mNPH dose.Significant increases were also made to a larger number of genetic and protein pathways related to immunity and cytotoxicity.According to this investigation, low-dose mNPH and radiation alone significantly boost the expression of immunological and cytotoxic genes; however, their combined effects are far more pronounced. (Duval et al., 2019).

In one work, magnetite (Fe3O4) nanoparticles were created by simultaneous deposition and then spread throughout a poly (vinyl pivalate) thermoplastic matrix using emulsion polymerization. Using polymerizable carboxylic acids as coating agents, the primary objective of separate encapsulation of MNPs was to reduce NP leaching during nanocomposite formation and improve the magnetic response of polymeric magnetic materials. In order to assess cytotoxicity levels against various cell lines (such as fibroblasts, keratinocytes, and human melanoma), Fe3O4's acidic agent size provided a saturation magnetization amount of nearly magnetic composites. This resulted in acceptable results at different times and concentrations of exposure, leading to more than 70% cell survival in comparison to the control group (Marzi et al., 2022).

The objective of this work is to mechanically evaluate the possibility that titanium dioxide (TiO2) nanoparticles can enhance the effects of chemotherapy in rat melanoma models both in vitro and in vivo. Following exposure to several doses of TiO2 NPs and/or cisplatin, the F10 melanoma cells' growth, viability, and mortality were evaluated.By inducing autophagy and necrotic cell death, cisplatin's antiproliferative and cytotoxic actions on F10 melanoma cells are enhanced by nontoxic doses of TiO2 NPs (50 μg/ml). Using rat embryonic fibroblast cell line as a model for cancer cell proliferation, it was determined that there was statistically substantial (very significant) inhibitory action for these cancer cells' development. The findings demonstrated the responsiveness of ZnO-NPs to (morphological) changes in the amount, shape, and dimensions of linear B16 cancer cells for melanoma.(Marzi et al., 2022).

CHAPTER FIVE

Conclusion

In the medical field, nanotechnology has created a new avenue for overcoming various obstacles related to traditional methods of curing skin cancer.

Because of their capacity to act as drug carriers, tumor-targeting molecules, anticancer agents, skin permeability enhancers, and other functions, nanoparticles are considered to be promising candidates for the treatment of skin cancer.On the other hand, topical (gel, cream, and microneedles) and non-invasive techniques can effectively cure skin cancer lesions in their early stages without having many dangerous side effects.It is regrettable that there are still no approved nano-based treatments for skin cancer, despite all these advantages. With this study, it is anticipated that commercial nanotherapeutics, akin to the commercial nanoformulations now in use for other diseases, would soon be available for the treatment of skin cancer (Siebert et al., 1996).

Here, we carried out a comprehensive evaluation of developments in the application of nanoparticles for advanced cutaneous carcinomas. Much new information on the active and passive targeting of cancer cell populations has been made possible by the development of NP-based delivery methods. Although their self-healing qualities are still being investigated, there is no doubting the potential advantages of NP-based treatments. Significant progress in the creation of multifunctional, stimuli-responsive, and mutation-selective NPs is probably not far off. Future research should focus on clarifying the mechanism, risk factors, and protective in vivo responses associated with hazardous NP aggregation and breakdown (Zeng et al., 2023).Topical-based nanoparticles are now undergoing different phases of clinical research and have not yet been utilized to treat skin cancer, despite the fact that several oral and systemic NP-based drug delivery systems are employed to treat skin cancer. Since this rapidly developing technology has the potential to push the boundaries of topical nanoparticle-based drug delivery, knowledge and insights from recent advancements in

formulation science can act as a guide for further improvements. According to the indication, it is critical to choose the appropriate medication (i.e., the particular anti-cancer drug for the particular sort of skin cancer), carrier (e.g., the NP), and formulation for cutaneous distribution. the possible use of nanoparticles' ability to assemble within hair and skin follicles. (Krishnan & Mitragotri, 2020).

CHAPTER SIX

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