

Review Article

A Review Of Various Methods Of Treating Skin Cancer Based On The Use Of Bio-Based Materials.

Andisheh Mahmoudian

Department of HSE, university of applied science and Technology, Semnan, Iran.

Abstract

The most common type of cancer in humans is skin cancer. This disease begins with the growth of cells on the skin and develops as they spread to other parts of the body. The causes of its occurrence include exposure to sunlight, hereditary factors, genetic mutations, and skin color. The outward signs of this disease include new bumps or rough spots on the skin, chronic wounds, changes or discoloration of moles and freckles, itching or pain around the skin growth. Types of skin cancer include basal cell carcinoma, melanoma, non-melanoma skin cancer, squamous cell carcinoma of the skin. Common methods of treating skin cancer include cryotherapy, surgery, electrodesiccation, chemotherapy, photodynamic therapy, immunotherapy, etc. Due to the negative impact of the above methods on the structure and physiological depth of the body and the occurrence of unpleasant clinical complications such as diarrhea and vomiting, pain, hair loss, digestive problems, loss of appetite, and skin discoloration, in recent years, extensive research has been conducted to use various methods such as natural and traditional techniques, alternative and complementary methods with the aim of reducing treatment outcomes and controlling stress and improving patients' mood. Some herbal medicines effective against skin cancer include turmeric, bloodroot, milk thistle, green tea, and berberine. Alternative and complementary methods such as dietary changes, exercise, meditation, homeopathy, and acupuncture have also been used. The latest research shows that biological materials are effective in the treatment of skin cancer. In this study, an attempt has been made to introduce a new generation of bio-based compounds and various gels for repairing skin cancer. Research shows that biological materials and their derivatives can play a significant role alone or as combined methods in limiting and eliminating skin tumors.

INTRODUCTION

The skin is the largest organ of the body and protects the body from environmental factors. The skin is composed of two main layers: the epidermis and the dermis. Skin cancer begins in the epidermis and is made up of squamous cells, basal cells, and melanocytes (1). Skin cancer is the most common type of cancer, and fair-skinned people are more susceptible to it because they have less melanin in their skin (2). Skin cancer is known as the most malignant type of cancer, and its melanoma type causes the highest death rate (3). Skin cancer is divided into 3 groups: Basal cell carcinoma, Squamous cell carcinoma, and Melanoma (4). Non-melanoma skin cancer is more common than melanoma, but melanoma is more dangerous (5).

Non-melanoma skin cancer is divided into two categories: BCC and SCC (6). Basal cell carcinoma is the most common type of skin cancer that occurs in the outer layer of the skin and causes visible signs such as red spots, open sores, and shiny bumps on the skin. Squamous cell carcinoma occurs

when abnormal cells begin to grow uncontrollably in the outer layer of the skin. Clinical signs of this type of cancer include red, scaly patches with open sores and can also bleed. Clinical signs of melanoma are mole-like growths that are usually black or brown but can also be blue, pink, red, or even white (4).

Factors contributing to skin cancer include exposure to sunlight, viruses, mutagens in food and chemicals, genetic susceptibility, age, sex, environmental carcinogens, immune suppression, organ transplant history, family history, certain infections, tanning bed use, vitamin levels and occupational exposure (7).

MATERIALS AND METHODS

General introduction to skin

The human skin, the outer covering of the body, is the largest organ of the body. It also forms the first line of defense. The skin is composed of many specialized cells and structures. It is divided into three main layers. The epidermis, dermis,

***Corresponding Author:** Andisheh Mahmoudian, Department of HSE, university of applied science and Technology, Semnan, Iran,

Email: andisheh.mahmoodian@gmail.com.

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and hypodermis. Each layer plays a distinct role in the overall function of the skin. The epidermis, the outermost layer of the skin, varies in thickness in different areas of the body. The thickness of the dermis varies depending on the location of the skin. The dermis is attached to the underlying hypodermis, or subcutaneous connective tissue. The subcutaneous tissue is a layer of fat and connective tissue that houses larger blood vessels and nerves. This layer is important in regulating the temperature of the skin and the body itself. Hair follicles, sweat glands, and sebaceous glands are the main appendages of the skin. The skin protects the underlying muscles, bones, ligaments, and internal organs. Since the skin is in contact with the environment, it plays a key role in protecting the body from pathogens, including (8):

- ✓ Sweating water from the skin surface when conditions are unusual for the body
- ✓ Insulating the body against changes in environmental temperature
- ✓ Helping to regulate body temperature
- ✓ Storing and synthesizing vitamin D using ultraviolet (UV) radiation and protecting vitamin B folates
- ✓ Absorbing oxygen and drugs and resisting water
- ✓ Helping to heal wounds by creating connective tissue
- ✓ Presence of pigments and skin color changes

Skin cancer

Skin cancer is defined as a malignant lesion of the skin, which is divided into two main categories (9): A) Keratinocyte carcinoma (non-melanoma): BCC and SCC

B) Melanoma cancer: Merkel Cell Carcinoma, Kaposi sarcoma and cutaneous lymphoma

C) There are other types of skin cancer, such as Merkel Cell Carcinoma, Kaposi sarcoma and cutaneous lymphoma, but they are considered rare (4).

The clinical symptoms of skin cancer vary from person to person and depend on the physiological and environmental conditions of the patient. Areas such as the scalp, neck, face, lips, chest, arms and hands, and legs are more susceptible to the disease. People with dark skin are more susceptible to skin cancer. (10).

Melanoma is a serious form of skin cancer. It develops in melanocytes. More than 70 percent of melanomas develop near brown moles on the skin (11). Although melanoma is treatable in its early stages, its advanced form is still a challenge. Some opportunistic pathogens can also cause skin cancer lesions (12).

Traditional methods in treating skin cancer

The use of natural methods for treating skin cancer is significant and has yielded relatively favorable results. There is a growing interest in using alternative and complementary medicine to treat skin cancer. Phytochemicals from various

parts of plants are used in the form of herbal teas and home-made tinctures for treatment (6). Some of the common natural methods include:

A) Turmeric: The active compound in turmeric, called curcumin, has anti-inflammatory properties and helps inhibit the growth of skin cancer cells (12).

B) Bloodroot: A herb native to North America. This plant contains a compound called sanguinarine, which has anti-cancer properties and can cause programmed cell death of skin cancer cells (12).

C) Dietary changes: Consuming certain foods and including them in a patient's diet can be effective in improving cancer. These include vegetables such as broccoli, spinach, and kale, which strengthen the body's defense mechanism. On the other hand, reducing the consumption of foods such as sugar and processed food ingredients can inhibit the growth of cancer cells (12).

D) Detoxification: This method plays an important role in improving the body's immune system. Consulting with specialist doctors and nutrition experts is very important. Consuming natural fruit juices and some detoxifying substances and appropriate nutritional supplements with the advice of experts helps to improve cancer (12).

E) Milk thistle: The active compound in milk thistle called silymarin helps improve liver function and has a detoxifying role in the body. The anti-cancer properties of this substance have been researched (12).

F) Green tea: The detoxifying and anti-inflammatory properties of this substance are well known. Green tea contains polyphenols, kanchins and EGCG, which inhibit the growth of cancer cells (12).

G) One of the plant derivatives effective against melanoma is berberine. This substance is a natural isoquinolone alkaloid in combination with doxorubicin, which acts on human melanoma and suppresses tumor growth. Also extracts of *Tilia amurensis* and *Camellia sinensis* were tested on skin cancer cells and were found to have cytotoxic effects (6).

Popular treatments for skin cancer

In addition to the various and common methods of treating cancer, some activities can provide a better fight for the patient to fight cancer. Some of these activities include (12):

- ✓ Acupuncture: A traditional Chinese method of inserting thin needles into specific points on the body that has been shown to reduce the side effects of radiation and chemotherapy for skin cancer patients and has shown promising results (12).
- ✓ Homeopathy: The use of highly diluted herbal medicines to stimulate the body's own ability to heal itself. The results of this method in treating skin cancer vary from person to person (12).
- ✓ Naturopathy: The use of non-invasive methods is

effective in improving cancer. These methods include lifestyle modifications, herbal supplements, and dietary changes. These methods are effective in treating skin cancer (12).

- ✓ Mind-body therapies: Using techniques such as meditation, yoga, and relaxation techniques can promote a sense of well-being in the body and also help the patient mentally fight cancer (12).
- ✓ Massage and Physical Therapy : Massage and physical therapy can help you manage chronic pain from melanoma. If melanoma has spread to your lymph nodes, strength training and stretching from physical therapy can be beneficial (11).
- ✓ Acupressure : The goal of acupressure is to release blocked energy in the patient's body and, by applying pressure to specific points on the body, helps a person with skin cancer recover (11).

Conventional methods of treating skin cancer

Treatment methods for cancer have various advantages and disadvantages, and their selection is influenced by factors such as the type of cancer and the patient's condition [6]. Conventional treatments for skin cancer include surgery, radiation therapy, and chemotherapy. The goal of these methods is to destroy cancer cells (13):

- ❖ Surgery: Helps cure the disease by removing the cancerous mass and surrounding healthy layers. This method is used for non-melanoma treatment (13). Surgery is the mainstay of treatment for skin cancer, but tumor recurrence and postoperative inflammation are still a challenge (14). After surgery, maintaining tumor size and preventing metastasis is a necessity for patient survival (15).
- ❖ Radiation therapy: This method uses high-energy X-rays or other rays to kill and shrink the cancerous mass. It is often used as a primary treatment for basal cell carcinoma and squamous cell carcinoma, as well as a supplementary treatment for melanoma (15).
- ❖ Chemotherapy: This method uses drugs to eliminate cancer cells. The drugs used can be in the form of lotions, creams, and injectable and oral medications (12). Side effects of chemotherapy include mouth sores, hair loss, appetite loss, nausea, diarrhoea, vomiting, liver and kidney dysfunction, neurological side effects, and decreased bone marrow activity (16). Chemotherapy is the main treatment for metastatic melanoma, but its effectiveness is low. Drugs such as dacarbazine, paclitaxel, temozolomide, carmustine, carboplatin, cisplatin, and vinblastine are used to treat skin cancer (17). Imiquimod 5% cream is used to treat superficial BCC on the skin. Another drug for treating skin cancer is tazarotene, which is used for minor cases of BCC (18).
- ❖ Immunotherapy : Immunotherapy, in the context of cancers, involves the use of various drugs to stimulate the immune

system to target cancer cells. Immunotherapy is being increasingly used for cutaneous malignancies, especially melanoma. Types of immunotherapy include passive and active (19).

- ❖ Photothermal Therapy: A treatment that utilizes laser or light therapy to heat and destroy cancer cells. This method uses non-ionizing near-infrared light to generate heat and destroy tumor cells (12).
- ❖ Combination Therapy: The combination of different treatment modalities to maximize the effectiveness of treatment (12).

Integrative and complementary approaches to skin cancer treatment

Complementary and alternative medicine is not considered a classic method of cancer treatment, but it is considered a part of healthcare that can help fight the disease (20). Complementary therapies for all types of cancer include a range of interventions that improve quality of life, such as dietary changes, exercise, homeopathy, hypnotherapy, and meditation. (21). In this method, if the treatment program is used instead of conventional cancer treatment methods, it is considered an ((alternative therapy)) and if it is used to help with the main treatment, it is considered a ((complementary method)) (22).

- ❖ Hyperthermia: Used as an adjunctive strategy with chemotherapy, radiotherapy and immunotherapy for cancer control. In this method, the temperature inside the tumor is increased to 60 degrees Celsius, leading to direct necrosis in the central area of the tumor. It also increases the level of drug absorption and has a positive effect on the body's immunity. (23).
- ❖ Marine compounds: Extracts of sponges, algae, and marine cyanobacteria have anti-cancer effects. Compounds extracted from these aquatic organisms include laminarans, fucoidans, alginic acids, and carrageenans, and play a role in cancer treatment (6).
- ❖ Microbial-derived compounds: Used to stimulate immune responses in cancer. This group includes anthracyclines, bleomycins, staurosporines, and actinomycins (6).

Application of hydrogels and biomaterials in the treatment of skin cancer

Conventional chemotherapy-based treatments for skin cancer have unpleasant side effects. In recent research, the development of a local drug delivery mechanism on the skin surface with in vivo activity, non-invasive and traceable, has been considered, reducing negative side effects for the patient (24). In this regard, new generations of biomaterials are emerging, including:

- A. Nanogels: Complex compositions of cross-linked

polymers at the nanoscale have emerged for targeted drug delivery and will create a platform for changing the therapeutic paradigm. The classification of these biomaterials includes cross-linked physical gels, liposome-modified nanogels, micellar and hybrid nanogels, and even plant-based nanogels (25).

- B. Hydrogels are three-dimensional networks that absorb water up to hundreds of times their dry weight (26). The use of hydrogels in cancer treatment has been developed due to their potential in drug delivery (27). The most important advantages of hydrogels in intensifying the fight against cancer include sustained release, targeted delivery, protection of therapeutic agents, and encapsulation of the drug in the hydrogel matrix, which allows the cancer cell to be exposed to the local effect of the drug for a long time. Hydrogels can be loaded with photosensitizers for treatment. Some photosensitizing drug molecules such as porphyrins, phthalocyanines, and chlorins have been investigated and have shown tumor-destructive effects (28).
- C. One strategy to enhance the effectiveness of hydrogel-based treatments involves the development of nanomaterialhydrogel composites. These composites provide controlled multi-stage release of therapeutic agents and leverage the unique properties of nanomaterials within the hydrogel system, resulting in improved synergistic effects for the combination therapy. Injectable hydrogels have demonstrated particular efficacy in delivering anticancer drugs and have played a crucial role in gene therapy, cell therapy, phototherapy, and combination therapy systems, as evidenced by various studies (29).
- D. the components of Bacillus Calmette-Guérin, BCG bacterium in gel form are effective in controlling skin cancer tumor growth . they have developed a new type of heat-sensitive hydrogel, which can be administered easily and in one go. This hydrogel is liquid at room temperature, but becomes a viscous gel at body temperature, thus acting as a local depot and continuously releasing components of the bacteria. This leads to a lasting activation of the immune system. Local application of the hydrogel is an effective and safe immunotherapeutic option to reduce the metastatic burden and prolong the survival of melanoma patients (30).
- E. hydrogels have gained more attention as 3D models for easier and faster screening of cancer and tumors due to their potential in mimicking the extracellular matrix (31).
- F. Polymer hydrogels with a three-dimensional network structure and self-healing properties, while delivering drugs to the tumor site and controlling their release,

reduce the toxic effects of the drug and increase its shelf life. Among these, iron-containing hydrogels have shown special functionality (32).

- G. Today, injectable hydrogels are also used to treat skin cancer around and within tumors because they provide maximum bioavailability of the drug at the desired site (33).
- H. In recent years, the combined use of immunotherapy with biomaterials has been effective for the treatment of melanoma. In this approach, hydrogels can be loaded with nucleic acids, cytokines, peptides, and antibodies, and can improve the effectiveness of melanoma immunotherapy (34).

Some effective methods in the treatment of skin cancer

- The use of BRAF inhibitors is effective for the treatment of melanoma. Photodynamic therapy relies on a light-activated compound and shows favorable results in tumor control (35).
- To reduce the adverse effects of chemotherapy and radiotherapy on patients with skin cancer, some drugs of natural origin that can have a preventive effect and contribute to skin beauty have been considered, including polyphenolic compounds, flavonoids, vitamins, alkaloids, terpenoids, isothiocyanates, carotenoids, ceramides and cannabinoids (36).
- Since the effectiveness of chemotherapy for the treatment of melanoma is limited, nanotechnology-based therapeutic methods are used. In this technique, the use of liposomes, nanofibers, carbon nanotubes, metal nanoparticles, and polymer nanoparticles has been considered for the treatment of skin cancer (7).
- Photodynamic therapy: This effective and non-invasive method uses lasers and photosensitizers to treat skin cancer. The patient is first given a photosensitizer and then exposed to a laser. This method, along with topical medications, can treat skin cancer (37).

RESULTS

Hydrogels offer excellent biocompatibility, biodegradability, drug loading and controlled release of drugs and are widely used in cancer radiotherapy, chemotherapy, immunotherapy, hyperthermia, photodynamic therapy and photothermal therapy (26). the hydrogel material can improve the targeting of the loaded drug to reduce the dose of the drug and improve the treatment efficiency (38).

In general, hydrogels based on polymer origin are divided into natural, synthetic, and A brief background on the hydrogel system for the management of skin cancer Novel shapes of treatment are needed to attack cancer cells while reducing the side efficacies of healthy cells . The development of a drug

delivery system for effective skin cancer treatment in which we can track in vivo activity non-invasively is highly desirable, primarily with the aim of avoiding or reducing side effects (24). Therefore, engineering injectable hydrogels by physical or chemical cross-linking for sustained and controlled drug release at in situ (near cancer) upon minimal injection enables higher drug concentration at the targeted site while diminishing the systemic drug concentration and the associated site effects (39).

plant-derived compounds have proved to exhibit DNA protection, antioxidant, anti-inflammatory, chemopreventive, and chemotherapeutic activities and could represent a promising alternative. Therefore, wound dressings consisting of biopolymers as the regenerative component and natural anti-cancer agents as the cancer recurrence-preventing component could represent ideal candidates to use for regenerative applications in skin cancer (40).

Hydrogels are evenly distributed at the tumor site, reducing drug consumption. They also accelerate drug penetration into the skin. The effect of nanoparticle-based hydrogels is effective in the treatment of melanoma. Examples of these compounds are transfersomes and liposomes (41). Injectable hydrogels with antineoplastic structures are a desirable option for intratumoral delivery. Due to the contrasting physicochemical properties of these materials with the surrounding environment and the human body, they undergo a gelation process, creating a large reservoir of anticancer agents (41).

DISCUSSION

Side effects of common skin cancer treatments such as chemotherapy and radiation therapy can cause itchy skin, nausea, fatigue, hair loss, joint and bone pain, gum and mouth ulcers, changes in body weight, skin reactions such as skin discoloration, diarrhea, and loss of appetite in patients (42). Common chemotherapy drugs also have limitations, including low efficacy, high doses of the drug in a short time, poor drug targeting, and high cost, which weaken the body's metabolic system (35). In recent years, drugs with natural bases and biological structures have been developed for the treatment of skin cancer (43). The use of drugs produced with nanotechnology and based on biopolymers has good potential for the treatment of cancer wounds by providing synergistic solutions to conventional treatments (45). The use of biotechnology in the treatment of skin cancer has also expanded, relying on nanoparticles (inorganic, polymeric, and lipid-structured). The effect of these materials in increasing the permeability and controlled and localized effectiveness of the drug has made them a desirable option in the treatment of skin cancer. Drug delivery routes can be carried out through topical treatment (cream, gel, etc.), intravenous

injection, intratumor injection, oral administration, etc (44). However, the use of biomaterials for the treatment of skin cancer also has limitations. These materials, as foreign organisms, can cause inflammation in the body. Also, their stability, mechanical properties, and strength require further research (1).

CONCLUSION

As stated in this study, various new, complementary and alternative methods for treating skin cancer were introduced with the aim of reducing the side effects caused by conventional methods. From the use of plants and marine organisms as traditional treatments to the use of methods such as acupuncture, changing the diet, exercising, doing healthy hobbies and spending more time with friends, they were presented. Also, research conducted on biomaterials and biotechnology technology for the effective treatment of skin cancer and with the aim of reducing drug consumption, maintaining the effect of the drug, etc. has shown that this technique is very significant. However, the important point is that many of the methods mentioned, which are used separately or in combination in the skin cancer treatment process, require further research because some of them, especially traditional treatment techniques, lack a written standard approved by reputable scientific societies in the world.

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