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Review article

A review on emerging herbal nanotechnology for skin cancer

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ABSTRACT

Many phytochemicals such as tannins, terpenoids and flavonoids are hydrophilic in nature, but have low absorption, because they are unable to cross lipid membranes of cells. It has been proposed to combine phytomedicine to nanotechnology, because nano carrier can deliver active phytochemical during entire treatment period, directing it to the desired site of action. The main aim of this work is to review Phytochemicals which possess promising anti-carcinogenic capabilities in a variety of skin cancer cell lines, animal models and their mechanism of action. The commercial formulations for skin cancer prevention and therapy that are now on the market that is derived from plants are also covered in this review. This paper focused on the recent assessment of the biological obstacles to topical applications of phytoconstituents and also focuses on review of the enormous potential for bioactive phytochemical distribution via developing nanotechnology.

Keywords: Melanoma, Nanotechnology, Herbal, Skin Cancer, Nanocarriers, Phytomedicine.

INTRODUCTION

The occurrence of skin cancer is constantly rising in nations where these tumours are common, and cancer is thought to be one of the leading causes of death worldwide. According to the World Health Organization, skin carcinoma is the fifth most frequent cancer in the world as of 2020 [1], and estimated skin cancer suggests that is the most prevalent type of cancer in the USA. The most often diagnosed malignancies in Caucasians worldwide is skin cancer, and its frequency is steadily rising as a result of increased exposure to ultraviolet (UV) radiation [2]. In addition to viruses, genetic vulnerability, mutagens in chemicals and in food, UV radiation is the primary reason of skin cancer [3,4]. By restricting or removing these triggers, skin cancer can be avoided. Anti-angiogenesis, a technique that effectively stops blood flow to the tumour, slows tumour growth, and prolongs patient survival, can be used to treat skin cancer. The majority of cancer cells learn to avoid dying or have flawed apoptosis systems, which permits uncontrollable cell growth [2]. Therefore, the primary target of chemotherapeutics anti-cancer is apoptotic process. Currently, skin cancer can be removed surgically or treated with chemotherapy, radiation treatment, or cryosurgery, among other methods. Choosing treatment is never a simple option because each treatment approach has benefits and drawbacks. The preferred option is determined by a number of factors, including the location of the cancer, the patient's health, and the opinions of the patient and doctor. The development of multi-drug resistance and significant side effects are the key issues with chemotherapeutic drugs. Drug efflux systems,

amplified targets of drug, or altered drug kinetics are a few ways that cancer cells can develop resistance to treatments [5]. The use of complementary and alternative medicines (Herbal) i.e., CAM has increased as a result of the limitations of conventional cancer chemotherapies and the purported advantages of more natural treatment modalities [6]. Plant roots, barks, bulbs, stems, leaves, and other plant extracts contain phytochemical substances that have shown promise as anti-cancer medications or as lead molecules in the manufacture of novel pharmaceuticals. They are frequently used in the form of teas, homemade tinctures, or unprocessed extracts as traditional remedies. Natural products and conventional medicines have drawbacks, such as variations in preparation techniques and, therefore, chemical composition, dosage estimation and modification, and the most appropriate route of administration. Even if there is a lot of study on natural chemicals to create novel pharmacological substances, it has become crucial to focus on naturally derived medications to optimise dosages for the intended route of administration and build the most efficient dosage forms [7].To combat drug resistance, and to avoid side effects a number of approaches have been tried, with some success, including the use of nanoparticles, liposomes, and micellar drug delivery vehicles [5].

The development of innovative nanosized delivery methods has been noteworthy in recent years. These systems may improve the penetration and absorption of herbal bioactive compounds via biological membranes, hence increasing their bioavailability. Phytosomes are an emerging nanotechnology that can be used to improve the miscibility of bioactive phytoconstituents in lipid-rich barriers and overcome their poor bioavailability. So, in present review we have emphasized on skin cancer malignancies, conventional formulation of skin cancer treatment, herbal remedies and different formulation system of delivering the phytoconstituents. The main contribution of this study is that it is first time that such compilation of skin cancer malignancies their conventional treatment and herbal approach with nanotechnology is conducted.

The key contributions of this paper are therefore summarized below:

- Skin cancer and their types
- Conventional therapy and approved drug for treatment
- Herbal remedies for skin cancer and other cancer malignancies
- Nanotechnology importance in delivery of active phytoconstituents with special emphasize on phytosome.

Skin cancer

One of the most predominant cancers in the last ten years is skin cancer [8]. Given that the skin is the largest organ of the body, it makes sense to consider skin cancer to be the most prevalent kind of cancer in people [9]. Melanoma and nonmelanoma skin cancer are the two main groups into which it is typically divided [10].

A dangerous, uncommon, and fatal form of skin cancer is melanoma. The American Cancer Society reports that although melanoma skin cancer accounts for only 1% of all occurrences, it has a higher mortality rate [11]. Melanocytes are the cells where melanoma grows. It begins when normal melanocytes start to proliferate uncontrollably and form a malignant tumour. Any part of the human body may be impacted. It typically develops on the hands, face, neck, lips, and other exposed parts to the sun's rays. Melanoma-type malignancies can only be treated if they are discovered early; if not, they spread to other body parts and cause the victim to suffer a torturous death [12]. There are numerous melanoma skin cancer subtypes, including lentigo maligna, acral lentiginous, and nodular melanoma. Nonmelanoma categories like basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and sebaceous gland carcinoma encompass the majority of cancer cases (SGC). In the intermediate and upper layers of the epidermis, BCC, SGC, and SCC, respectively, are generated. The likelihood of these cancer cells spreading to other bodily parts is very low. Compared to melanoma cancers, nonmelanoma cancers are simpler to cure. Early diagnosis is therefore crucial for skin cancer treatment [13]. The biopsy approach is typically used by doctors to find skin cancer. Through this treatment, a sample of a potentially malignant skin lesion is removed for testing by a doctor. This procedure is difficult, cumbersome, and slow. Researchers are searching for efficient anticancer medications with fewer side effects in order to combat the sickness due to the alarming and horrifying rise in the number of people dying from various types of skin cancer. Because finding specific chemotherapeutic medications that destroy or render

malignant tumour cells harmless while having no effect on healthy cells is the ultimate goal of anticancer therapy[14]. But tragically, modern chemotherapeutic treatments for cancer also destroy healthy cells. Therefore, there is an urgent need for new, more potent, and non-toxic natural products, such as phytochemicals having anticancer characteristics [15].

Medicinal herbs have been used from the beginning of time. Accessibility-wise, therapeutic substances originating from plants provide a lot of benefits. They are used to treat and prevent a number of fatal illnesses, such as AIDS, hepatitis, and cancers[16]. Research into new phytochemicals for cancer treatment and prevention has increased as a result. Phytochemicals, in particular, have become popular alternatives to conventional therapies due to their affordability, accessibility, and low toxicity [1]. The search for anticancer medications derived from plants started when vinca alkaloids' anticancer properties were identified in the 1950s. Consequently, numerous plants with anticancer potential have undergone substantial research [17]. Indirect or direct links to natural sources have been found in 40% of all FDA-approved pharmaceuticals to date [18].

Phytomedicine for skin cancer

There are several natural resources that can be used for medical purposes that are available all over the world, many have not yet been fully utilised for potential use in pharmaceutical sector. Over half of all medications currently in the market have some natural source of origin, including over seventy percent of anti-cancer treatments. Plants, marine life, animals, and microorganisms are examples of natural sources [19]. Due to their accessibility and abundance, plants continue to be the primary natural source for novel medications and lead compounds and are the most often used natural resource in pharmaceutical science. Only a few naturally derived medications that treat skin malignancies are now available on the market; none have been given the go-ahead for topical use. The known negative effects of these substances when applied topically to the skin may be to blame for this. With an emphasis on melanoma, the sections that follow provide an overview of substances from various natural sources that have been discovered to display activity against various forms of cancer.

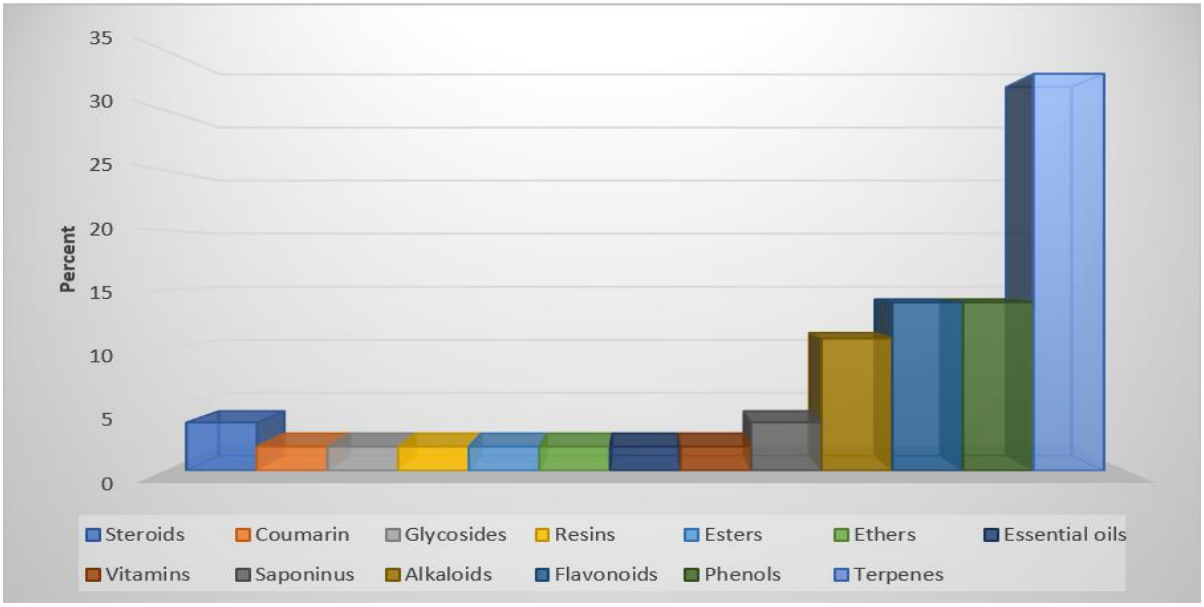
The primary plant-derived anti-cancer substances to receive clinical approval were the vinca alkaloids, which include vincristine, vinblastine, and vinorelbine. After that, the taxanes (paclitaxel and docetaxel), podophyllotoxin derivatives (etoposide and teniposide), and camptothecin derivatives (irinotecan and topotecan) were discovered and approved [17, 20]. The vinca alkaloids work by interacting with tubulin to prevent the formation of the mitotic spindle, which kills cells that are actively dividing as a result[20]. Taxanes function by stabilizing the microtubule rather than disrupting it, in contrast to vinca alkaloids. Microtubule stabilization causes an imbalance between microtubules and tubulin, which impairs regular cellular activity and ultimately leads to cell death. Although podophyllotoxins and camptothecins block topoisomerase I in different ways, they both interfere with cell division [19]. Table 1 shows various cytotoxin phytochemical to different cancer lines.

Table 1: Cytotoxin phytochemicals to different cancer cell lines

Ref	Plant Name	Cancer Cell line/Animal Model	Part Use	Phytochemical
[21]	Cirsium japonicum	S180, H22 (liver cancer)	Leaf	Pectolinarin
[22]	Hibiscus mutabilis	HepG2, MCF7	Seeds	Lectin
[23]	Emblica officinalis	L929	Fruit	Pyrogallol
[24]	Plumbago zeylanica	A549, PC3, A375 (skin cancer), NB4 (blood cancer), SGC7901	Roots	Plumbagin
[25]	Piper nigrum	B16F10 (melanoma)	Seeds	Piperine, piperidine
[26]	Tylophora indica	A549, DU145, ZR751 (breast cancer)	Leaf	Tylophorine
[27]	Pothomorphe umbellate (Piperaceae)	SK-MEL103, SK-MEL2, SK-MEL147	Whole	4-nerolidylcatechol
[28]	Zingiber officinale	Epidermoid carcinoma cells A431	Rhizome	[6]-Gingerol (phenolic ketone)
[29]	Robiniapseudoacacia (Fabaceae)	SK-MEL5, SK-MEL28 in mice	Whole	Acacetin (flavonoid)

40 percent of the therapeutic drugs currently in use that have received FDA approval are either directly or indirectly derived from natural sources[30]. This review focuses on the anti-carcinogenic efficacy of plant-derived components on a variety of skin cancer cell lines as tabulated in Table 1, and there in vivo testing on preclinical animal models. In addition, a brief description of skin cancers' phytochemical epidemiology shown in Figure 1.

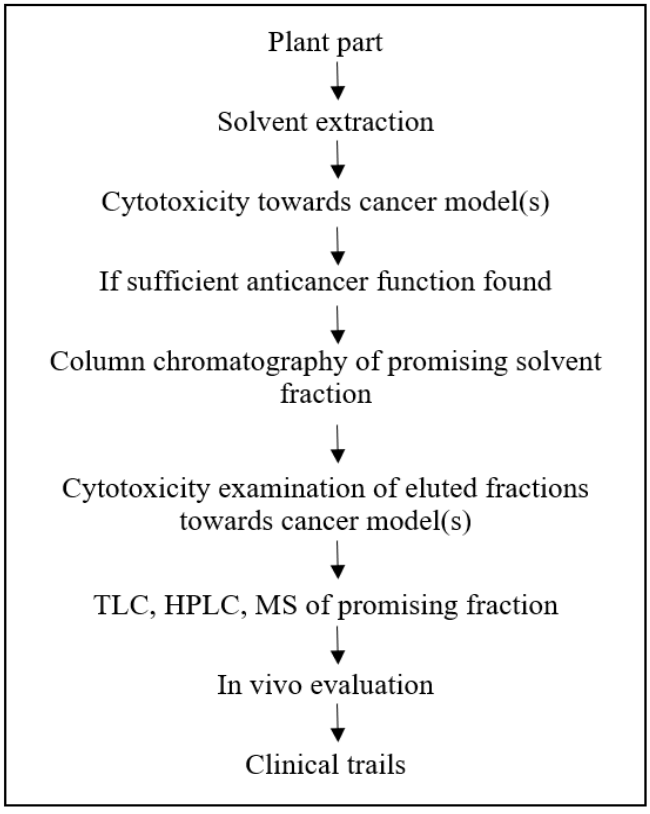
Figure 1: Percent inhibition - skin cancer cell line of various phytochemical class.



Purification of anticancer phytochemicals development process

The fractionated active extract using the proper matrices, the eluted fractions are assessed for bioactivity, and the active fractions are studied using a number of analytical techniques, such as mass spectrometry, FTIR, thin layer chromatography (TLC), and HPLC (MS). Also, this method can be used to purify chemicals that are antibacterial, antilipolytic, and antioxidant (Figure 2).

Figure 2: Bioactive phytomolecule(s) development into an anticancer product[31]



Nanotechnology platform for the delivery of bioactive phytochemicals

Nanosized drug delivery devices can be used to increase the bioavailability of phytocompounds by enhancing their penetration across biological barriers and overcoming the limited absorption of bioactive polyphenolic phytocompounds [32-34]. In comparison to traditional phytochemicals made at other scales, nanocarriers play a crucial role in preventing oxidation and degradation of the bioactive polyphenolic phytochemicals, preserving their long-term benefits and enhancing their stability [35]. When phytochemicals are applied topically, the large nanoparticles surface area enhances the efficient delivery of active substances into skin [36].

Liposomes and polymeric nanoparticles go into the organic delivery system category, while silver, gold, and copper nanoparticles fall into the inorganic delivery system category [37]. Liposome is one of the most popular nanoparticles effectively applied in the cosmetics and pharmaceutical industries [38]. In compared to free curcumin, liposomal nanoparticles encapsulating curcumin demonstrated strong anticancer efficacy against pancreatic, lung, and colorectal cancer at lower dose [39]. Polymeric nanoparticles can be used as effective nanocarrier of phytochemicals. Silver and other metallic inorganic nanoparticles have also been employed as phytocompound nanocarriers. When made into silver nanoparticles, ginseng herbal extract had higher anticancer activity in vitro against A549 cells at lower dose [40]. Moringa oleifera showed strong therapeutic effect against the in vitro

model of non-small cell lung cancer when delivered by gold nanoparticles [41].

Phytosomes are one of these newly developed nanotechnologies that can be used to improve the miscibility of bioactive phytoconstituents in lipid-rich barriers and overcome their poor bioavailability [42]. Summary of recent studies on different nanocarrier used in skin cancer therapy is shown in table 2.

Table-2: Summary of recent studies of various nanocarrier for skin cancer therapy.

Aim	Nanocarriers type	Used Polymer	Cell Line/Animal Model	Drug	Result	Ref.
To create a vemurafenib-loaded liposome modified with a peptide for the targeted suppression of subcutaneous melanoma delivered through the skin.	Liposomes	DSPE-PEG-NHS, Lecithin, cholesterol,	Human A375 melanoma Cells, Murine B16F10 melanoma Cells, Human umbilical veinendothelial cells (HUVEC), Male BALB/cmice (Baggalbino mouse)	Vemurafenib	A375 cells successfully ingested liposomes with Vem's targeted suppression of cancer cells. At a lesser concentration, liposomes exhibited the required anticancer properties.	[43]
To create an EGFR-targeted immunoliposome containing 5-FU, enabling the simultaneous administration of the antibody and the chemotherapy, and achieving SCC-specific distribution.	Liposomes	DSPC, DSPE-PEG-Mal, cholesterol,	SCC xenograft animal modelEGFR-positive SCC cells, Porcine ear skin	5-FU, cetuximab	Immunoliposomes have greater absorption and penetration than liposomes. Compared to 5-FU solution, tumours in immunoliposomes shrank after iontophoresis.	[44]
To investigate artemisone's niosomal formulation's anti-melanoma properties	Niosomes	Span 60, cholesterol	A-375 (human malignant melanoma cell), HaCaT (human epidermalkeratinocytes)	Artemisone	Niosomes boost anticancer activity while being barely harmful to healthy skin.	[45]
To look at the application of niosomes as 5-FU topical delivery methods for treating skin cancer.	Niosomes	Cholesterol, hexadecyl-bis- (18-crown-6, 1-aza-), Span 80	SKMEL-26 (human melanoma cell) HaCaT (human epidermal keratinocytes)	5-FU	Niosomes boosted anticancer activity and percutaneous permeability by eight times.	[46]
To look for ways to treat actinic keratosis and non-melanoma skin cancer with improved 5-FU skin absorption.	Transfersome	PC, Tween-80, Span-80	Dorsal skin of mice (Swiss albino male mice)	5-FU	Better drug deposition and trapping were demonstrated via transfersomal gel.	[47]
Tocopherol-loaded transfersome research must be conducted in order to assess its antioxidant and skin-regenerative abilities	Transfersome	Soy PC, alphatocopherol acetate, Tween-20, 40, 60 and Tween -80	One-day old pigs' dorsal Skin, Human epidermal Keratinocytes, Mouse embryonic fibroblast	Alpha-tocopherol	With an antioxidant effect, the transfersome utilising Tween-80 had the highest entrapment efficiency and smallest vesicle size.	[48]
To investigate the use of carvedilol-loaded transfersomes in the prevention of skin cancer.	Transfersome	SPC, sodium Cholate, DSPC, Tween-80, HEPC,	Porcine ear skin, Mouse epidermal cell line, 3D Human Reconstituted Skin Model	Carvedilol	In comparison to a free medication with a photoprotective action, drug penetration for transfersome was lower.	[49]

Phytosomes - significance in topical drug delivery

Phytosomes are a cutting-edge lipid-based delivery method with a structure similar to liposomes that can be utilized to entrap various phytoconstituents with polyphenolic bases to increase their absorption when administered [50]. Indena business (Milan, Italy) created the first phytosomes in the late 1980s with the intention of increasing the bioavailability of medications by complexing them with phospholipids. The phosphate group of the phospholipid's matrix and the polyphenolic moiety of the bioactive herbal extracts engage via an H-bond to form the lipid vesicles of phytosomes in non-polar solvents [51]. The development of nanotechnology-based phytosomes may have an impact on medicine delivery by removing obstacles caused by inadequate lipid solubility and enhancing the bioavailability of bioactive phytochemicals including silybin, ginkgo, and Polyphenolic substances present in olive oil. The active component of milk thistle, silybin, is a water-soluble flavonoid with strong antioxidant and hepatoprotective properties [52]. However, silybin is poorly soluble and absorbed in a biological membrane that is rich in lipids. When milk thistle extract was packaged into a phytosome delivery system, it was more readily absorbed and displayed seven times as much antioxidant activity as free silybin [53]. Additionally, oral administration of a silybin phytosome formulation to rats demonstrated a notable improvement in bioavailability [54].

Ginkgo herbal extract was delivered via phytosomes nanotechnology, which showed positive effects on the pharmacokinetic profile and improved brain and vascular protection [55]. In compared to the free extract, the Gingko biloba extract's flavonoids and terpene components were much

more absorbed when it was included in a phytosomes delivery system, according to a study done on human volunteers [56]. Oleaselect is a manufactured product made from phytosomes that is based on the polyphenols in olive oil. When administered as a phytosomal formulation as opposed to conventional oil, anti-inflammatory, antioxidant, and antihyperlipidemic action, as well as cardiovascular protection, were reported to be increased [57]. The effects of Green select herbal extracts included inhibiting the production of pro-inflammatory cytokines, free radical scavenging, antioxidant activity, and other advantages. According to reports, Green select's formulation as Phytosomes increased this extract's bioactivity and bioavailability [58].

Conclusion and Future Prospects

Natural products are becoming more and more popular because of their affordability and superiority over existing medications' adverse effects. The development of phytopharmaceuticals against severe metabolic syndromes, including cancer, is the focus of increased research. Every year the affected people worldwide by the skin cancer are millions in number. Over the past few decades, intensive research has resulted in the development of numerous synthetic anti-cancer medications. However, the bulk of the population prefers to employ natural medicines due to their high cost and considerable negative effects. The only requirement is to develop the better system for desired action of Phytomedicine. The creation of herbal nanoparticle drug delivery systems for the treatment of cancer by fusing conventional phytomedicine with contemporary nanotechnology may draw research teams in the future. Promising therapies that enhance people's health may result from this collaboration.

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