Review Article

Skin cancer and role of herbal medicines

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Abstract

Skin cancer is the uncontrolled growth of abnormal skin cells. It occurs when unrepaired DNA damage to skin cells and triggers mutations, or genetic defects, that lead the skin cells to multiply rapidly and form malignant tumors. This is an increasing problem as the lifestyle, habits and environment changes occur. Various treatments for malignant melanoma are available, but due to the development of multi-drug resistance, current or emerging chemotherapies have a relatively low success rates. This review emphasizes the importance of discovering new compounds that are both safe and effective against melanoma. Herbal Medicines are now significantly studied and use for the treatment of skin cancers worldwide.

Keywords: Skin cancer, carcinoma, Melanoma, herbal Treatment

Introduction

Skin cancer is the uncontrolled growth of abnormal skin cells. It occurs when unrepaired DNA damage to skin cells which is most often caused by ultraviolet radiation from sunshine triggers mutations, or genetic defects, leads to the skin cells to multiply rapidly and form malignant tumors. Skin cancers are the most frequently diagnosed malignancies in Caucasians worldwide, whilst their incidence keeps increasing, due to increased exposure to ultra-violet (UV) radiation. Cancer of the skin is characterized by an imbalance towards too little apoptosis, or too much cell proliferation and survival in the epidermis (Lippens et al., 2011). Although UV radiation is the leading cause of skin cancer, other causative agents include viruses, mutagens in food, mutagens in chemicals and genetic susceptibility (Marks and Hanson, 2010; Freedman, 2007).

The main problems with chemotherapeutic agents are the severe adverse effects and multi-drug resistance. Many Methods which cause cancer cell to resistant to chemotherapy are drug efflux systems, amplification of drug targets, or changes in drug kinetics (Iyer et al., 2013; Kunjachan et al., 2013; Markman et al., 2013). Various strategies have been attempted to overcome drug resistance, such as the use of nanoparticles, liposomes and micellar drug delivery vehicles, with some reported successes. The adverse effects of cancer chemotherapy can be treated symptomatically, which is unacceptable to some cancer patients (Alifrangis et al., 2011; Thornton et al., 2011).

There has been a growing interest in the use of complementary and alternative medicines, due to the disadvantages associated with conventional cancer chemotherapies and the supposed advantages of more natural treatment options (Molassiotis et al., 2005). Phytochemical compounds from extracts of plant roots, bulbs, barks, leaves, stems and others have shown promising potential as anti-cancer drugs, or for serving as lead compounds in the synthesis of new drugs. They are often utilized as traditional medicines in the form of home-made tinctures, teas, or crude extracts. Limitations with natural products include variation in preparation methods and therefore also chemical composition, dosage determination and adjustment, and the suitable route of administration.

Types of skin cancers

There are three major types of cancers: Basal Cell Carcinoma (BCC), Squamous Cell Carcinoma (SCC), and Melanoma. The first two skin cancers are grouped together as non-melanoma skin cancers (NMSC). Non-Melanoma Skin Cancer (NMSC) is the most frequently diagnosed skin cancer.

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is an epithelial malignancy that occurs in organs that are normally covered with

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squamous epithelium which includes several different anatomic sites, including the skin, lips, mouth, esophagus, urinary tract, prostate, lungs, vagina, and cervix (Yan et al., 2011). SCC is more common in males than in females, the postulated reason behind it is more exposure of sun light to the males due to outdoor works. An individual who is fair skinned or fair haired are more susceptible for Squamous Cell Carcinoma

Numerous genetic alterations have been described in SCC sub-types, although the molecular mechanisms contributing to tumor initiation and progression are still poorly understood.

Head and neck squamous cell carcinomas

Head and neck squamous cell carcinomas (HNSCC) make up the vast majority (more than 90%) of head and neck cancers and rank as the sixth most common cancer worldwide. They are a group of tumor entities that arise from squamous mucosal surfaces, including nasal cavities, paranasal sinuses, oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx.

Esophageal squamous cell carcinoma

Esophageal cancer (EC) ranks as the eighth most common cancer, with the sixth highest mortality in the world (Kamangar et al., 2006; Parkin et al., 2005). As the predominant histological subtype of esophageal cancer, esophageal squamous cell carcinoma (ESCC) contributed 80% of all esophageal cancers worldwide. ESCC is characterized by extreme diversity in geographical distribution and high mortality.

Non-small cell lung carcinomas

NSCLC are classified into four histologic subtypes: squamous cell carcinoma (SCC), adenocarcinoma (ADC), large cell carcinoma, and sarcomatoid carcinoma. Anatomically, about 70% of SCC present as central lung tumors whereas adenocarcinomas generally present as peripheral lung tumors.

Symptoms and signs to early diagnosis of Squamous Cell Carcinoma:

- Rough or scaly red patches, which might crust or bleed.
- Raised growth or lumps, sometime with a lower area in the center.
- Open sores (which may have oozing or crusted area) that don't heal, or the heal that come back.
- Warts like growth.

Aetiology for SCC

- Excessive exposure to UV lights is the main factor.
- Chronic infection and skin inflammation.
- HIV infection.
- Immune deficiency diseases.
- Chemotherapy
- Anti-rejection drugs used during organ transplantation.
- Exposure to chemicals like Arsenic, Paraffin, coal tar and some oils.
- Human Papilloma Virus (HPV) infection.
- Xeroderma Pigmentosum (XP)
- Psoriasis treatment.
- Smoking.

Treatment Options for SCC

- Mohs Surgery
- Excision surgery
- Curettage and electrodessication (electro surgery)
- Cryosurgery
- Laser Surgery
- Radiation Therapy
- Photodynamic Therapy (PDT)
- Topical Medication

Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common type of skin cancer (75% to 80%) and the most common of all cancers. Basal cell carcinoma may originate from the epidermis or from the upper portion of hair follicles, grows in dermis as chords, strands or sheets of small, uniform basaloid cells, with scant cytoplasm and large, round and elongated nuclei. BCC develop in the basal cell layer of the epidermis. Exposure to sunlight may cause DNA damage (thymine dimer formation). While DNA repair removes most UV-induced damage, not all cross-links are excised. Thus, cumulative DNA damage occurs. Apart from the mutagenesis, sunlight decreases immune surveillance for new tumor cells. A gene commonly found to be mutated in BCC is the PTCH gene. A PTCH gene mutation at chromosome 9q22.3, which inhibits the hedgehog signaling pathway, is found in patients with basal cell nevus syndrome (Gorlin syndrome). Similarly, a mutation in the SMO gene (hedgehog pathway) also causes basal cell carcinoma (Voon Hoff, 2009).

There are several subtypes of BCC. The following are the main subtypes:

- **Nodular BCC** is the most common subtype. It usually develops on areas of the face exposed to the sun. Nodular BCC appears as a round, raised, pink, red or pearly white lump or an area with wide blood vessels showing on top.
- **Superficial BCC** is the 2nd most common subtype. It usually develops on the central part of the body (trunk), arms or legs. Superficial BCC appears as a pink or red

scaly area.

- **Infiltrative and micronodular BCCs** usually develop in the head or neck area. They grow deeper into the skin and into the inner layer of the skin (dermis). Infiltrative and micronodular BCC can look like nodular BCC. They grow and spread more quickly than nodular and superficial BCC.

Symptoms and signs to early diagnosis of BCC

Usually grow on areas that get the most sun light, such as the face, neck and head. But they can grow anywhere in the body

- Flat, firm, pale or yellow areas, similar to a scar.
- Raised reddish patches that might be itchy.
- Small, pink or red, translucent, shiny, pearly bumps, which might have blue, black or brown areas.
- Growth with raised edges and a lower area in their center, which might contain abnormal blood vessels spreading out like spokes of the wheel.
- Open sores (which may have oozing or crusted area) that don't heal, or the heal that come back.
- A persistent, non healing sore is a very common sign of an early BCC.

Etiology of BCC

- Ultraviolet rays exposure leads to DNA damage and mutation
- Human Papiloma virus (HPV)

Treatment Options for BCC

- Mohs surgery
- Chemotherapy (5-FU, imiquimode)
- Radiation Therapy

Melanoma

The most dangerous form of skin cancer, these cancerous growths develop when unrepaired DNA damage to skin cells (most often caused by ultraviolet radiation from sunshine or tanning beds) triggers mutations (genetic defects) that lead the skin cells to multiply rapidly and form malignant tumors. These tumors originate in the pigment-producing melanocytes in the basal layer of the epidermis. Melanomas often resemble moles; some develop from moles. The majority of melanomas are black or brown, but they can also be skin-colored, pink, red, purple, blue or white. Environmental exposure (UV light) plus genetic susceptibility (CDKN2A, CDK4, MC1R, BRAF, p16/ARF genes) leads to the accumulation of genetic mutations in melanocytes that activate oncogenes, inactivate tumor suppressor genes and impair DNA repair mechanisms. This leads to melanocyte proliferation, blood vessel growth, tumor invasion, evasion of immune response, and ultimately metastasis (Thompson et al., 2005).

Two genes conferring susceptibility to melanoma have been identified within high-risk families, *CDKN2A* and *CDK4* (Hussussian et al., 1994; Zuo et al., 1996). Both of these genes are important in controlling cell division. *CDKN2A* codes for two proteins, p16 important in the retinoblastoma pathway, and p14ARF, important in the p53 pathway. Melanoma arises by pigment producing melanocytes that migrates to the skin and eye from the neural crest during embryologic development. Approximately 5% melanoma occurs in non-cutaneous site such as the eye and mucous membrane of the orophyrynx, sinuses, vagina and anus.

Clark levels of invasion

Level I: Limited to the epidermis

Level II: Invades papillary dermis

Level III: Extends to papillary-reticular dermal junction

Level IV: Invades reticular dermis

Level V: Invades subcutaneous fat

Eitiology of Melanoma

- UV / sunlight exposure
- Dietary Factors (Smoke, alcohol, Poly unsaturated Fat)
- Benpyrene and Other Chemicals
- Viruses (Ocorna Virus, HaMV Retro virus, Herps virus)

Treatment of Melanoma

- Surgical excision (cutting it out)
- Mohs Micrographic Surgery
- Immunotherapy
- Chemotherapy
- Radiation Therapy
- Biochemical treatment (Interleukines, Interferons, Tyrosine Kinase)

Other types of skin cancer are very rare, these are

- **Kaposki Sarcoma (KS)** - is caused by human herpes virus. This cancer usually appears as lesion or tumors on the skin. Tumors may also form in mouth, lungs and digestive tract. KS appeared in immune-compromised individuals.
- **Cutaneous Lymphoma** – is a type of non-hodgkin lymphoma. This rare cancer may appear as a rash or bumps on the skin.
- **Keratoacanthoma** – are typically benign tumors that grow slowly and often go away on their own. This carcinoma is often treated like a form of SCC.

Herbs in the treatments of skin cancer

A variety of treatments are available for non-melanoma skin cancers with good outcomes, especially if the cancers are detected and treated in the early stages of development.

However, there are some serious disadvantages with the most common treatments. Some disadvantages of current treatments are these treatments are moderately painful, slow healing, scarring, specialized training by health professionals with appropriate facilities, expensive, activity restriction after surgery if skin graft or flap is needed, limited cosmetic results (Bill, 2011).

There are numerous reports of cancer chemo-preventive activity of dietary botanicals, including cruciferous vegetables such as cabbage and broccoli, Allium vegetables such as garlic and onion, green tea, Citrus fruits, soybeans, tomatoes, berries, and ginger, as well as medicinal plants. Several lead compounds, such as genistein (from soybeans), lycopene (from tomatoes), brassinin (from cruciferous vegetables), sulforaphane (from asparagus), indole-3-carbinol (from broccoli), and resveratrol (from grapes and peanuts) are in preclinical or clinical trials for cancer chemoprevention. Phytochemicals have great potential in cancer prevention because of their safety, low cost, and oral bioavailability. In this review, we discuss potential natural cancer preventive compounds and their mechanisms of action.

Eggplant

The glycoalkaloids solasodine rhamnosyl glycosides (SRGs) induce apoptosis in a wide variety of cancer cells **(**2004, Shiu et al., 2007; Shiu et al., 2008; Sun et al., 2010). SRGs are present in a diversity of solanaceous plants such as the Devil's Apple (*Solanum linnaeanum*) and Eggplant (*S. Melongena*). SRGs display specificity towards cancer cells when compared with normal cells and the unique mode of action has been described (Daunter and Cham, 1990).

Anticancer therapies with SRGs in animals and humans have been used intravenously (Milward, 2006), intraperitoneally, intralesionally (Cham, 2008) and topically (Cham, 2007; Cham et al., 1991; Punjabi et al., 2007). A constant mixture of SRGs, known as BEC, consisting of solasodine containing triglycosides solasonine (β-solatriose) (33%), solamargine (β-chacotriose) (33%), and di-and monoglycosides (34%), are present in a cream formulation which contains 0.005% BEC (Curaderm). Curaderm is reportedly effective for treating nonmelanoma skin cancers as shown by uncontrolled and controlled studies (Punjabi, 2007).

SRGs have previously been shown to have good anticancer properties and are superior to other anticancer agents such as taxol, cisplatin, gemcitabine, camptothecin, vinblastine, methotrexate, 5-fluorouracil, epirubicin and cyclophosphamide (Shiu, 2007). The mode of action of SRGs is unlike any current antineoplastic agent. Specific receptors for the SRGs present only on cancer cells but not normal cells are the first step of events that lead to apoptosis in cancer cells only, and this may explain why during treatment the cancer cells were being eliminated and normal cells were replacing the killed cancer cells with no scar tissue being formed.

It was subsequently shown that very low concentrations of BEC, as low as 0.005% BEC, were effective in treating skin cancers. However, in order to obtain efficacy with this very low concentration of BEC in a cream formulation CuradermBEC5, salicylic acid (10%) and urea (5%) had to be added to the cream. These substances acted as keratolytic agents which enabled BEC to have access to the cancer cells.

Olive Oil

Olive oil comes from the fruits of *Olea Europaea* trees. It consists mainly of oleic acid, with smaller quantities of other fatty acids such as linoleic acid and palmitic acid. More than 200 different chemical compounds have been detected in olive oil, including sterols, carotenoids, triterpenic alcohols, and phenolic compounds. Hydrophilic phenols are the most abundant antioxidants of olive oil.

In a murine study with UVB radiation, extra virgin olive oil applied to the skin delayed the onset and reduced the incidence of skin cancer development, likely secondary to reduced number of 8-hydroxy-20 -deoxyguanosine (8-OHdG) positive cell formation (a biomarker of oxidative stress and carcinogenesis) (Budiyanto et al., 2000).

Sunflower Oil

Sunflower seed oil originates from the seeds of *Helianthus annus*. The components of sunflower oil mainly consist of oleic and linoleic acids. Sunflower seed oil contains relatively higher linoleic acid concentration relative to olive oil. This property makes sunflower oil a suitable ingredient in skin products due to the positive benefits of linoleic acid. Sunflower seed oil also exhibited a chemopreventive effect in a murine model of skin cancer with two-stage carcinogenesis. Sesamol, one of its constituent, specifically play a role in the chemopreventive effects (Kapadia et al., 2002).

Grape seed Oil

Grape seed oil comes from the seeds of Vitis vinifera. It is rich in phenolic compounds, FFAs, and vitamins. (Zhao et al., 1999**).** extracted proanthocyanidins in grape seeds after grape seeds were air-dried and made into a powder. They demonstrated that proanthocyanidins in grape seeds had a strong inhibitory effect for UVB-induced skin tumor development in SENCAR mice.

Mice that consumed proanthocyanidins had reduced tumor size (29%–94%), tumor incidence (20%–95%), and tumor multiplicity (46%–95%) for UVB-induced stages of photocarcinogenesis. Furthermore, they found that through in vivo and in vitro systems, photoprotection was a result of antioxidant mechanisms (Mittal et al., 2003).

Sesame oil

Sesame seeds contain significant amounts of lignans such as sesamin, sesamolin,and sesamino. , sesame oil showed a chemopreventive effect in a murine model of skin cancer with two-stage carcinogenesis. Its constituent, sesamol, has also been demonstrated to play a role in chemoprevention (Kapadia, 2002). Topical sesame oil also protects the skin from UV radiation (Korac and Kambholja, 2011).

Pomegranate Seed Oil

A study of CD1 mice with topically applied pomegranate seed oil has shown that pomegranate seed oil (5%) significantly decreased tumor incidence and 12-O-tetradecanoyl-phorbol-13-acetate (TPA)-induced ornithine decarboxylase activity in the chemical-induced skin cancer model. The results highlighted the potential of pomegranate seed oil as a chemo-preventive agent against skin cancer (Hora et al., 2003).

Red Clover Oil

It is thought that red clover helps cells to regenerate and, traditionally, it has been used in combination with other herbs to help with cancer treatment by using either a tea or tincture internally combined with local poultice applications externally, if needed. Because it helps cells regenerate and has anti-inflammatory properties, it is also good for external applications to heal wounds and skin complaints such as eczema, psoriasis, and acne.

The 95% ethyl alcohol extract of one of these actives, TrÃ¬folium pratense L. Leguminosae, red clover, significantly inhibited the metabo lism of B(a)P and decreased the level of binding of benzo(a)pyrene to DNA by 30 to 40%. Using activity-directed fractionation by solvent partitioning and then silica gel chromatography, a major active compound was isolated and identified as the isoflavone, biochanin A. The pure compound decreased the metabolism of benzo(a)pyrene by 54% in comparison to control cultures and decreased benzo(a)pyrene - DNA binding by 37 to 50% at a dose of 25 Â«ig/ml. The ability of the isoflavone biochanin A to inhibit carcinogen activation in cells in culture suggests that in vivostudies of this compound as a potential chemopreventive agent are warranted (John et al., 1988).

Silibinin

Silibinin has multiple targets in the cell, and can be protective against the harmful effects of cytotoxic agents such as reactive oxygen species and inflammation. Further, silibinin modulates mitogenic and survival signalling, p53, Cip1/p21 and other cell cycle regulatory molecules to prevent UVB-induced skin carcinogenesis. Our ongoing studies also suggest the positive effect of silibinin on the repair of UVB-induced DNA damage in mouse skin. Overall, the protective efficacy of silibinin against skin cancer is supported by sound mechanistic rationale in animal and cell culture studies, and suggests its potential use for humans (Singh and Agarwal 2005).

Resveratrol

Resveratrol, a phytoalexin antioxidant found in red grapes, has been shown to have both chemopreventive and therapeutic effects against many diseases and disorders, including those of the skin. Studies have shown protective effects of resveratrol against ultraviolet radiation mediated oxidative stress and cutaneous damages including skin cancer. Because many of the skin conditions stem from ultraviolet radiation and oxidative stress, this antioxidant appears to have promise and prospects against a wide range of cutaneous disorders including skin aging and skin cancers.

Resveratrol, a trihydroxy derivative of stilbene (3,5,4'-trihydroxystilbene), is a naturally occurring phytoalexin antioxidant present in grapes, berries, peanuts and red wine (Ren and Lien, 1997).

Carcinogen-treated mouse mammary glands in culture, and (ii) tumorigenesis in a chemically-induced skin carcinogenesis mouse model (Jang et al., 1997). Since the appearance of this study in the year 1997, evidence accumulated from a plethora of studies, both *in vitro* and *in vivo*, have suggested that resveratrol could be developed as a strong chemopreventive and/or therapeutic agent for the management of cancer (Adhnani, 2003; Ahmed, 2001; Afaq, 2003; Pezzuto, 2008).

In one another *in vitro* study demonstrated that resveratrol was able to induce apoptosis in two human melanoma cell lines, (Yang et al., 2008) showed that resveratrol inhibits APE/Ref-1 and significantly decreases AP-1/JunD, MMP-1, Bcl-2, and iNOS protein levels in melanoma cells.

or the first time, suggested that i) resveratrol imparts strong chemopreventive effects against UVB exposure-mediated skin carcinogenesis, and ii) the chemopreventive effects of resveratrol may, at least in part, be mediated via modulations in Survivin and other associated events (Aziz, 2005).

d-Limonene

The scientific basis to use d-limonene as an anti-cancer nutrient, especially for breast cancer prevention and treatment, is well established in literature (Miller et al., 2013). The regulating property of terpenes on the NF-κB signaling pathway, already documented for their anti-inflammatory

effects (Jhang, 2006; Alessio, 2013), is also believed to be one of the primary modes of operation for their anti-cancer properties. In fact, many nutrients can interact with the NF-κB signaling system in regulating cell growth, survival and apoptosis (Ong et al., 2012). From the known properties of d-limonene, it may be extrapolated that it uses its solvent properties to enter tumor cells and directly alter cell signaling and/or modulate free radical production, thereby favoring apoptosis.

Extensive human research on d-limonene and skin cancer is lacking, but some experimental data is, however, encouraging. Chaudhary et al. (2012) reported on the positive effect of d-limonene to reduce the tumor burden in a model of DMBA/TPA chemically-induced multistage mouse skin carcinogenesis model. They demonstrated that the effects of the monoterpene involved an increase in apoptosis, inhibition of oxidative stress and Ras-signaling.

Genistein

Genistein is a flavonoid found in soy, Greek sage, Greek oregano, and ginkgo biloba extract and is specifically a major isoflavone in soybeans. Studies have shown that genistein have antioxidant and anticarcinogenic activity in the skin (Wei et al., 2003) as well as protection against photodamage in mice (Shyong, 2002). Studies in mice have demonstrated that genistein inhibits skin carcinogenesis. Wei et al., 1998 demonstrated that genistein inhibited DMBA-initiated and TPA-promoted skin carcinogenesis by treating SENCAR (sensitive to carcinogenesis) mice with 10 micromoles of topical genistein for one week. A later study by Wei et al. found that topical genistein also reduced ultraviolet B-induced skin tumor multiplicity and incidence in hairless mice. Although there are no reported studies assessing the effect of genistein on human skin cancer development, genistein was found to inhibit UVB-induced photodamage in a small study of six men (Wei, 2003).

Curcumin

Curcumin (diferuloylmethane), a yellow colored substance from the root of the plant *Curcuma longa* Linn. It has been demonstrates to inhibit carcinogenesis of murine skin, stomach, intestine and liver (Kelloff, 1997; Huang, 1997).

In vitro studies have indicated that curcumin inhibits several TPA-induces signal transduction pathways (Nakamura et al., 1998; Lin, 1997). It has been reported that curcumin inhobits TPA-Induced activation of protein kinase C, formation of 8-hydroxy-deoxyguanosine and transactivation of c-jun/Ap-1 (Shih, 1993; Huang, 1991). Evidences suggest that curcumin acts on stages of initiation, promotion and progression of carcinogenesis (Huang, 1992; Shalini, 1987; Chen et al., 1998).

Daidzein

Daidzein is a soy isoflavone, which is highly soluble in alkaline environments and is part of a group of compounds, called phytoestrogens (Huang, 2008). It has demonstrated some chemo-protective potential in the skin, since topical application of daidzein in a study resulted in effective photo-protection (Lin, 2008). In vitro studies showed that daidzein was able to inhibit UVB induced production of hydrogen peroxide within cells and therefore the protection of the keratinocytes. Daidzein and genistein have been investigated as synergistic cytotoxic agents in various studies and evidence showed that the two isoflavones had worked well together (Huang, 2008; Wang, 2002). Franz cell based, in vitro diffusion studies and tape-stripping showed that minimal amounts of daidzein had managed to penetrate through the skin (Huang, 2008). This unfavorable skin permeation characteristic of daidzein may be the reason for the limited research that has been carried out with regards to its potential use as a topical photo- and chemo-protectan

Conclusion

We conclude from this review, that many naturally derived compounds become significant in future skin cancer treatments. This article has summarized some of the plants that have been studied to date for their possible anti skin cancer properties. Many more untapped resources, however, remain in nature. Natural products have shown the potential for use in the symptomatic treatment of skin cancer, or to treat the adverse effects associated with cancer therapies.

Conflicts of interest

All the authors are not having any conflicts of interest in this article.

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