REVIEW ARTICLE

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A review of selected natural phytochemicals in preventing and treating malignant skin neoplasms

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Abstract

Malignant skin neoplasms are one of the most common human malignancies. The incidence of nonmelanoma skin cancers and malignant melanoma is constantly increasing. The current therapies, especially for malignant melanoma, have relatively low success rates. Therefore, there is an urgent need to develop new remedies that are both safe and effective. Natural substances have always been an important source for the discovery of new therapies. In turn, a number of studies have indicated that some phytocheicals could have an anti-tumour effect. *In vitro* and *in vivo* testing of malignant skin neoplasm models revealed different anti-tumour actions, including antioxidation, carcinogen inactivation, anti-proliferation, cell cycle arrest, induction of apoptosis, inhibition of angiogenesis, or a combination of them. The aim of this paper is to describe anti-tumour compounds derived from natural sources that might be used in the therapy of malignant skin neoplasm. The phytochemicals discussed below include carotenoids, terpenoids and flavonoids.

Key words

nonmelanoma skin cancer, malignant melanoma, phytochemicals, carotenoids, terpenoids, flavonoids

INTRODUCTION

Malignant skin neoplasms are the most commonly occurring human malignancies. They are responsible for approximately 33% of diagnosed cancer cases. The incidence of both non-melanoma skin cancers (NMSC) and malignant melanoma (MM) has been constantly increasing in recent years. Among the various reported skin tumours, basal cell carcinoma (BCC), squamous cell carcinoma and malignant melanoma are the most frequently reported [1]. Basal cell carcinoma (carcinoma basocellulare, BCC) is the most frequently occurring skin malignancy and comprises 2/3 of all skin cancer. BCC belongs to the epidermal group of tumours that arise from the uncontrolled growths of basaloid keratinocytes [2]. The second most common cancer is squamous cell carcinoma (carcinoma spinocellulare, SCC). SCC is formed through uncontrolled proliferation of abnormal cells arising from the squamous keratinocytes. In general, it occurs on chronically sun-exposed areas of the body. SCC is locally invasive and has a potential to form metastasis to other tissue and organs [3]. BCC and SCC belong to the group of non-melanoma skin neoplasms. Despite the fact that the NMSC exhibit a high percent of occurrence, they are much less aggressive than potentially lethal melanoma [4]. Malignant melanoma is the most dangerous type of skin neoplasms, causing the majority (75%) of skin malignancy deaths. These tumors develop as a result of increased proliferation of damaged melanocytes [5].

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The process of transforming healthy skin cells into melanoma cells is incompletely understood. Several environmental and genetics factors have been identified. Epidemiological data indicate that the one of most important factors contributing to non-melanoma and melanoma skin neoplasms development is ultraviolet radiation (UV). UV causes a harmful effect by direct and indirect mechanisms, such as cyclobutane pyrimidine dimers formation, immunosuppression and oxidative stress [6]. Among the other factors that play a role in skin tumour formation are therapies, including radiotherapy, phototherapy and Psoralen Ultra-Violet A (PUVA) therapy. Another study has revealed that exposure to polycyclic aromatic hydrocarbons (PAH) and arsenic could have an impact on skin growths formation [7]. A linkage between the human papilloma virus (HPV) and squamous cell carcinoma formation has also been demonstrated [8]. In addition, genetic factors influence the carcinogenic process. Fair-skinned people, especially with red hair, are at higher risk; however, people with darker skin and other hair colours can also develop skin malignancy. Non-melanoma skin cancer occurrence is also associated with immunosuppression [7, 9]. Among the methods currently used in skin cancer therapy are surgical treatments, phototherapy, chemotherapy, radiotherapy and cryosurgery [10]. Each of these methods has their advantages and disadvantages. The main problems that exist with current therapies are adverse effects. Moreover, despite the numerous therapeutic strategies, the numbers of patients with melanoma continue to present poor prognosis. Therefore, the search for new anti-tumour drugs with higher efficiency and fewer side-effects should be continued. In view of the disadvantages linked with traditional skin malignancy therapies and capabilities of natural treatments, an increased

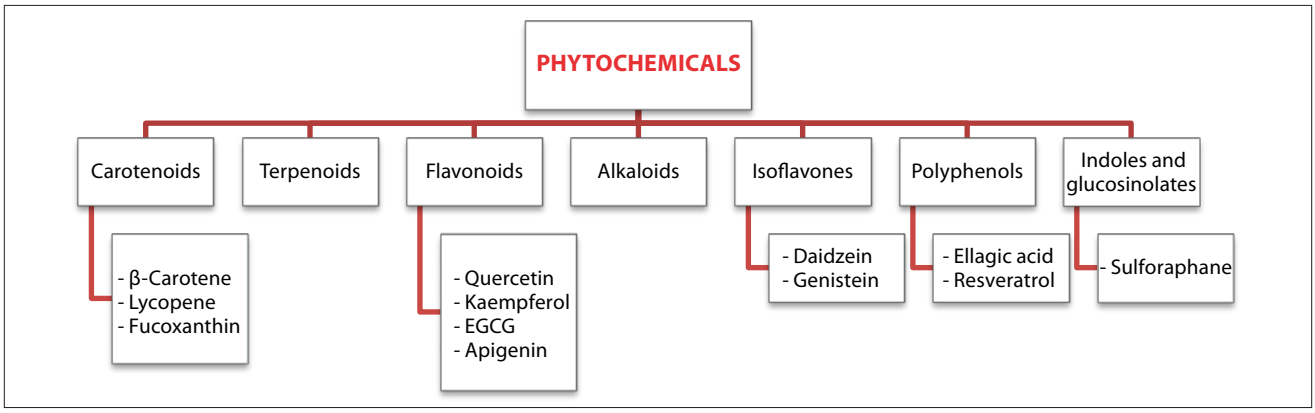

Figure 1. Classification of phytochemicals

interest in the use of complementary and alternative medicines has been observed [11]. Numerous reports have shown that several plants and herbs have anti-tumour activity [12, 13]. About 50% of drugs currently used in clinical therapies have been extracted from plants. It has been shown that a number of phytochemicals isolated from plant roots, stems, barks, leaves, and others parts, are promising for use as anti-tumour drugs, or as substrates in the synthesis of new drugs [14].

The word phytochemicalis derives from Greek, in which '*Phyto*' means plant. Phytochemicals are defined as bioactive, non-nutrient plant compounds, the activities of which reduce the risk of disease. These compounds can be divided into carotenoids, terpenoids, flavonoids, alkaloids, isoflavones, polyphenols, indoles and glucosinolates (Fig. 1) [15].

This review will discuss skin cancer treatment and prevention by means of phytochemicals, include carotenoids, terpenoids and flavonoids.

Carotenoids. To-date, over 600 carotenoids have been identified, of which about 60 are presence in our diet. Carotenoids are fat-soluble, natural isoprenoid pigments that can be found in fruits, vegetables and flowers. These compounds provide plant leaves with a distinct yellow, orange and red colour. They belong to a large family of polyisoprenoids, made up of eight C_5-isoprenoid units that are combined with C_{40}-tetraprenoids. Figure 2 presents the chemical structure of some carotenoids. According to differences in chain construction, carotenoids are divided into two groups. The first, called hydrocarbons, consists of compounds that contain only carbon and hydrogen atoms. These compounds are less polar and absorb radiation at a higher wavelength. The second group, known as xanthophylls, consists of compounds that contain at least one atom of oxygen. These compounds are more polar and absorb radiation with a lower wavelength [16, 17].

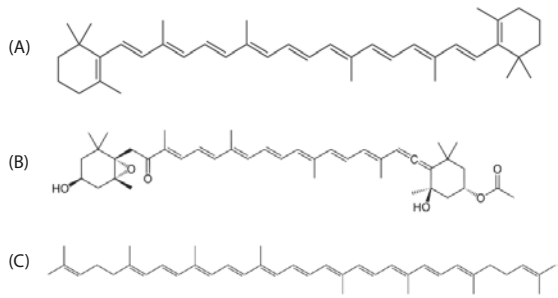

Figure 2. Chemical structures of β-carotene (A), fucoxanthin (B) and lycopene (C)

Numerous studies have been reported the medicinal properties of carotenoids, mainly its antioxidant activity that reduce DNA damage through free radicals and reactive oxygen species (ROS) scavenging. The most frequently studied and the most abundant carotenoid in the human organism is β-carotene [17]. β-carotene has anticancer properties and is involved in the inhibition of melanoma progression. Its activity is linked to the regulation of gene expression, induction of apoptosis and inhibition of tumour specific angiogenesis. Additionally, carotenoids are able to prevent induction of melanoma by protecting skin from damaging UV light exposure [18, 19]. The first promising *in vitro* results led to the assumption that β-carotene might be regarded as a highly protectant substance. However, subsequent controlled studies in human and animal models have shown contrary or ambiguous results with regards to anti-cancer *in vivo* results. Grenberg *et al.* followed-up the randomized patients with a recent nonmelanoma skin cancer. They received 50 mg of β-carotene or placebo daily for up to five years. Obtained results revealed no difference between the experimental and placebo groups, and β-carotene did not exhibit an anticancer effect on nonmelanoma skin cancer [20]. Further studies have indicated similar results. A twelve-year increased supplementation with β-carotene had a little or no effect on the incidence of malignant neoplasm in the first few years. There were 996 malignant neoplasms diagnosed in the β-carotene group, and 1,027 in the placebo group [21]. In another study, a diet high in sources of carotenoids, (yellow-coloured fruits and vegetables) had influence on the decreased risk on the incidence of melanoma. However, this effect may have been supported by other nutrients, for example, magnesium, vitamin E and vitamin C [22]. To sum-up to these findings, it is difficult to accurately assess the beneficial influence of carotenoids, including β-carotene, on the inhibition of skin cancer growth of formation *in vivo*.

Terpenoids. Terpenoids, also known as terpens or isoprenoids, are the largest group, and include over 20,000 of natural compounds. They are abundant in mosses, algae, lichens and other higher plants. These compound are formed from five-carbon isoprene units (C_5H_8) (Fig. 3).

According to the number of isoprene units, terpenoids are commonly devided to hemiterpenoids (C_5), monoterpenoids (C_{10}), sesquiterpenoids (C_{15}) diterpenoids (C_{20}), triterpenoids (C_{30}), tetraterpenoids (C_{40}) and polyterpenoids $(C_5)_n$. Terpenoids are minor components in our diet, but they exhibit a large biological activity against cancer or inflammation

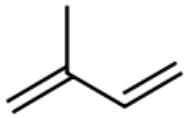

Figure 3. Isoprene units (C_5H_8)

[23]. The first commercial anticancer agent developed from terpenes was Taxol®, extracted from pacific yew (*Taxus brevifolia)*. It has been shown that terpenoids extracted from tea tree (*Melaleuca alternifolia*) oils are able to exhibit some anti-cancer activity, including basal cell (BCC) and squamous cell (SCC) carcinomas. Tea tree oil (TTO) in 10% dilutionin dimetyhyl sulphoxide (DMSO) exerted a cytotoxic effect on tumour cells with activation of immune cells when applied topically. Studies performed *in vivo* presented that 10%TTO/DMSO caused damage to tumour cells, such as mitochondrial membrane disruption, gross swelling and dissolution of internal structures. These results indicated that the application of diluted tea tree oil might be used for skin cancer therapy [24]. Also, Muto *et al.* have recommended using oleanolic oil, abundant in terpenes, for skin cancer therapy [25]. Ljubica *et al.* showed that terpenoides extracted from the most important medicinal mushrooms *Ganoderma lucidum* also exhibit strong antitumor activities. Both a methanol extract and a purified methanol extract, mainly containing acidic terpenoids, inhibited tumour growth of *in vitro* and *in vivo* melanoma models. The mechanism of this activity comprised an intensified production of reactive oxygen species, inhibition of cell proliferation and induction of apoptosis [26]. Such findings justify the possible application of terpenoids as a drug for the treatment of human skin tumours, and seems to be promising.

Flavonoids. Flavonoids are polyphenolic compounds that are ubiquitous in green cells and in the flowering parts of plants. The main dietary sources of flavonoids for human are fruits vegetables, tea or wine. They comprise a large group of natural compounds that are characterized by a benzopyrone structure. All flavonoids have the characteristic common phenylbenzopyrone structure (C6-C3-C6), and are categorized according to the degree of hydroxylation, other substitutions and conjugations, and degree of polymerization. Due to this, these compounds can be divided into main classes of flavones, flavanols, isoflavones, flavonols, flavanones, and flavanonols [27]. Numerous data from laboratory and epidemiological studies indicate that flavonoids have important effects on cancer chemoprevention. They exhibit many biological activities, including free radical scavenging capacity, carcinogen inactivation, anti-proliferation, cell cycle arrest, induction of apoptosis and inhibition of angiogenesis [28]. It has been found that flavonoids from citrus peels (CPE) demonstrate potential anti-tumour activity in the two-stage carcinogenesis skin model. These activities include inhibition of inflammation, proliferation, angiogenesis, and induction of apoptosis. Citrus peels are an abundant source of polyhydroxyl flavonoids (PHFs) and are almost the sole source of polymethoxyflavones (PMFs) [29]. Cibin *et al.* found that the topical application of flavonoids from the flowers of *Saraca asoka* could potentially be used in skin cancer therapy. Flavonoid fraction applied before treatment with corton oil (promoter), significantly reduced to 71% the occurrence of tumours in mouse. The authors suggested that flavonoids from plant extracts might be absorbed into the skin and activate a cascade of protective signaling pathway [30]. In another studies, it has been showed that silymarin (a unique flavonoid complex) extracted from the seeds and fruit of milk thistle (*Silybum marianum*) indicated protective and antitumour activity against skin cancer. It was found that silymarin could inhibit cell proliferation, induce growth arrest in G0-G1 and G2-M phases of the cell cycle and apoptosis. Other actions involved photoprotection by reactive oxygen species and free radicals scavenging, thus preventing photocarcinogenesis and skin cancer promotion [31]. Based on these results, flavonoids may be promising anticancer agents.

CONCLUSIONS

This article described some natural compounds abundant in vegetables and fruits that have been studied for their possible usage in anticancer therapy. The majority of above-mentioned studies indicate that phytochemicals could play a crucial role in skin cancer treatment. Several mechanisms have been proposed to explain how these natural compounds help to prevent neoplasms. These actions include carcinogen inactivation, anti-proliferative effect, cell cycle arrest induction, induction of apoptosis, inhibition of angiogenesis. Although the *in vitro* and *in vivo* studies on the anti-cancer properties certainly provide promising results for the compounds discussed in this review, controlled studies conducted in humans were not conclusive. The beneficial effects in skin cancer treatment caused by the above-described activities should be clinically proved. It is necessary to conduct large, randomized trials that would help to determine the effectiveness of plant medicines. Further knowledge is still needed about pharmacokinetics and the toxicity of phytochemicals. There is little information on long-term safety, drug interactions, ideal dosages and adverse effects. There are many advantages in using phytochemicals, but therapies based only on natural compounds are quite a challenge. It is still too early to draw conclusions about their anticancer properties.

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