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PHOTOCHEMOPREVENTION OF CUTANEOUS NEOPLASIA THROUGH NATURAL PRODUCTS

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Non-melanoma skin cancers such as squamous cell carcinoma and basal cell carcinoma are the most common types of human tumors, representing 30% of the new cases of malignancies diagnosed each year. Ultraviolet radiation (UV) from the sun is a major cause of non-melanoma skin cancer in humans. The prevention and mainly the photochemoprevention with natural products represent a simple but very effective strategy in the management of cutaneous neoplasia. Here we review the progress in the research of new and existing agents developed to protect the skin exposed to UV. We also discuss the current state of knowledge on their photosuppression mechanism in humans as well as in animal models, and efficiency in cancer prevention.
Key Words: **UV radiation, cancer, skin, chemoprotection, natural products.**

Skin carcinomas represent 30% of the new cases of malignancies diagnosed each year, and their incidence is continually increasing. The main factor incriminated in skin cancer is represented by the ultraviolet (UV) radiation, especially type B (UVB) radiation, which accounts for 90% of the skin cancer cases [1]. Each year over 1.3 million cases of skin cancer are being diagnosed in the United States [2]. The permanent increase of the pre-malignant and malignant lesions, the reduced efficiency of the photoprotective creams, the uncontrolled exposure to sunlight are the reasons of an increased interest in developing the new methods of skin neoplasia prevention.

The chemoprevention using natural products (polyphenols, monoterpene, flavonoids, indols, etc) represents a new concept in attempts to control the process of carcinogenesis: to prevent the development of the tumors, to slow down their progression or even to induce tumor regression [3, 4]. Some compounds from fruits, vegetables and other plants prolong the process of carcinogenesis [5]; they have anti-inflammatory, immunomodulatory and anti-oxidant property [6], which is making them the ideal chemoprevention agents of skin cancer.

This paper aims to review the main compounds currently used for skin cancer chemoprevention. Some of them are antioxidants (vitamin E, ascorbic acid, polyphenols, isoflavonoids), which protect the skin from the oxidative effects of UV radiation; others interfere with the process of DNA repair or modulate the immunosuppression induced by UV radiation [7]. To this day, there is no ideal compound that can provide complete protection of the tissue against UV radiation. Therefore, *in vivo* and *in vitro* studies are carried out to identify the target molecules and signalling pathways of different chemopreventive compounds, which would increase their applicability in clinical practice.

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Abbreviations used: 6-4PP – 6-4 pyrimidine-pyrimidone; AP-1 – activator protein-1; COX-2 – cyclooxygenase-2; CPD – cyclobutane pyrimidine dimer; EC – epicatechin; ECG – epicatechin-3 gallate; EGC – epigallocatechin; EGCG – epigallocatchin-3 gallate; EGF – epidermal growth factor; ERK – extracellular signal regulated kinase; IGF – insulin-like growth factor; iNOS – inducible nitric oxide synthase; JNK – c-jun N-terminal kinase; MAPK – mitogen activated protein kinases; MMPs – metalloprotease; NF-kB – nuclear factor-kappa B; p21 – cyclin-dependent kinase inhibitor 1A; PCNA – proliferating cell nuclear antigen; PUVA – photochemotherapy; STAT3 – signal transducer and activator of transcription 3; TNFα – tumor necrosis factor alpha; UV – ultraviolet; VEGF – vascular endothelial growth factor.

THE ROLE OF ULTRAVIOLET RADIATION IN CARCINOGENESIS

In 1894 Paul Gerson Unna established that there is a direct causal relationship between exposure to sunlight and the development of the cutaneous carcinomas. The UV radiation is a complete carcinogen because it initiates and promotes the tumor growth [4, 8]. In acute exposures it determines: erythema, oedema, burns, pain, the thickening of the epidermis and skin pigmentation [9], and after long and repeated exposures it leads to immunosuppression [1], premature ageing [10], and cutaneous carcinomas [11, 12].

The different wavelengths of UV radiation penetrate the skin differently and, therefore, exert different biological effects. Although UVB radiation (290–320 nm) represent 5% of the solar radiation, it is the most dangerous, because it can induce burns and skin cancers and can intervene in the initiation, promotion and progression of tumor [1, 13, 14].

As a result of the interaction between the UV photons and the DNA molecules, the DNA is transformed into excited state, in which the electrons are rearranged and two photoproducts with a dipyrimidinic structure are formed: the cyclobutane pyrimidine dimer (CPD) and 6-4 pyrimidine-pyrimidone (6-4PP) [7]. The development of these photoproducts interferes with DNA-replication, preventing its repair and leading to specific mutations. The most frequent mutations of DNA after UVB irradiation include the substitution

of cytosine base by thymine. It was noticed that the methylation of the cytosine residues in the 5'-CCG and 5'-TCG sequences increased the formation of CPD over 10 times, preferentially in *p53* gene [15].

Usually the photoproducts formed after irradiation are repaired effectively, but if the solar exposure is chronic and excessive, the process of repair is exceeded, the photoproducts persist and replicate, which may lead to transcriptional errors and, finally, to cancer [16]. The DNA lesions are repaired mainly by nucleotide excision repair (NER) [16]. This process is realised either by global genome repair (GGR), involved in the repair of any sequence in the genome regardless of its transcriptional status or by transcription coupled repair (TCR), involved only in the repair of actively transcribed DNA strands. The CPD repair is not sufficient, because UVB radiation can determine deletions and chromosomal aberrations [17].

Aside mutations, UV induces lipid peroxidation reactions in the membrane of keratinocytes [18], determines the oxidation of proteins, the isomerization of the trans-urocanic acid, intensifies the activity of metalloproteases (MMPs) in the dermis, determines the breakage of the double-strand DNA resulting in oxo-8-2'deoxyguanosine [19], and reduces the antioxidant capacity of the skin [10].

The chemical carcinogenesis and that determined by UVB is a complex process that takes place in well-defined stages: initiation, promotion and progression. The initiation stage is associated with the genotoxic effect of the UV on the normal cells. The promotion stage includes the clonal expansion of the cells that were initiated and is considered reversible, as opposed to the progression stage that needs other genotoxic stimuli to transform the benign lesions, namely the papillomas into carcinomas.

The mechanism by which UVB radiation induces promotion is not yet well understood, but it is considered that both the reactive oxygen species and also the activation of the signalling cascades intervene in this process, including the synthesis of prostaglandins, which determines the clonal expansion of the initiated cells [4, 20].

In the process of carcinogenesis, the immunosuppressive effect of the UV radiation has to be taken into account. The UV radiation induces modifications of the cellular mediated immunity: it decreases the numbers of circulating T lymphocytes, the T helper/T suppressors ratio decreases, the late onset hypersensitivity reaction is modified [21]. Moreover, the native Langerhans' cells in the skin are replaced by the population of hystiocytes with a distinct antigenic profile and with the capacity to stimulate the tumor suppressive T cells. The chronic exposure to sun induces the occurrence of inflammatory infiltrate, which is responsible for the sunburn reaction. It correlates positively with the high incidence of skin cancers and with premature ageing of the skin [22]. When administered in drinking water polyphenols from green tea noticeably reduce the inflammatory response in animals [23]. The similar effects were observed in humans [24]. For this reason, the prevention of UV-induced immunosuppression represents an important strategy in the management of skin cancers [24].

CHEMOPREVENTION

The target of chemoprevention is interruption of intracellular signals that transmit aberrant stimuli. The use of natural compounds such as polyphenols, monoterpene, flavonoids, organosulfides, indols as chemopreventive agents showed promising results, because they can influence on one or more stages of carcinogenesis [3, 25].

To this day 30 classes of chemical compounds with preventive effect were described, some of which are already used in clinics (Table 1). From these compounds, a special attention was offered to polyphenols. They proved their preventive effect in studies of different carcinogens. This is very important because pollutants, psychical stress, drugs, pesticides, UV radiation induce the large quantities of free radicals, which play an important role in the cancer development.

Polyphenols. In the last years the polyphenols found in the green tea were the most studied compounds because of their chemoprotective effect. More than 765 papers, devoted to the preventive effect of the green tea on tumors, were published [5]. There are four classes of polyphenols that were isolated from the *Camellia Sinensis*: epicatechin (EC), epicatechin-3 gallate (ECG), epigallocatechin (EGC) and epigallocatchin-3 gallate (EGCG). Among polyphenols

Table 1. Chemopreventive activity of plant-derived natural products in skin cancers

Plant	Active principals	Experimental model	Mechanism of action
Curcuma longa	Curcumin	DMBA-TPA-induced mouse skin papillomas	Suppression of extracellular signal regulated kinase activity and NF-kB [26]
	Curcumin	DMBA-induced skin papillomas	Antioxidant [27]
Ocimum sanctum	Leaf extract	DMBA-induced skin papillomagenesis in Swiss albino mice	Antioxidant and detoxification mechanisms [28]
Ocimum gratissimum	Clocimum oil	DMBA-induced skin papillomas	Antioxidant, elevation in hepatic and skin GST, sulfhydryl (-SH), cytochrome b5 activity [29]
Vitis vinifera	Proanthocyanidins from grape seeds	DMBA-TPA-induced skin tumourigenesis in mice	Suppression of ornithine decarboxylase, myeloperoxidase and proteinkinase C [30]
	Polyphenols from grape seeds	DMBA-TPA-induced skin carcinogenesis	Antioxidant [3]
	Resveratrol from grape seeds	skin cancer UV-induced in SKH-1 hairless mice	Inhibition of Survivin-phosphorylation and up-regulation of Smac/DIABLO in skin tumors [1]
Withania somnifera	Root extract	DMBA-induced papillomas in mice	Antioxidant [31]
Camellia sinensis	Polyphenols from green tea	UV irradiated SKH-1 hairless mice	Antioxidant [35]
		photocarcinogenesis in C3H/HeN mice	Induce IL-12 and prevent immunosuppression UV-induced [57]

the most abandoned is EGCG (50–80%) [5]. Other compounds were also identified, such as caffeine, flavandiols, phenolic acids and alkaloids, such as teobromin and teophilin.

Wang *et al.* [32] were the first who suggested that polyphenols from green tea might have a protective effect against the UV radiation. They showed that polyphenols administered superficially or in the drinking water of SKH-1 mice prolonged the proliferation of experimental tumors in a dose-dependent manner [32]. They decreased the DNA damage [14] and reduced the formation of CPD in the skin [33]. The green tea and its polyphenols assured a good protection against erythema, immunosuppression and photoageing of the irradiated skin [34]. They reduced the number of wrinkles and decreased the production of MMPs 2, 3, 7 and 9 [35]. EGCG inhibited the immunosuppression upon UV radiation and the production of reactive oxygen species in the skin macrophages $CD11b^+$ [23], and increased the number of Langerhans' cells.

Grapes are very rich in polyphenols, mainly the seeds (60–70%) that contain the derivative of flavan-3-ols called catechins. In contrast to polyphenols from the green tea that are monomers, those from grapes are dimers, trimers or oligomers, and are called procyanidins and proantocyanidins. Proantocyanidins from grape seeds are more potent antioxidants and scavengers for free radicals than the ascorbic acid or vitamin E [24]. Using the different carcinogenesis models, it was proved that they have an antitumor effect [36], and reduce the rate of papillomas transformation into carcinomas from 70% to 25% [24]. It was observed that the polyphenols from grape seeds exhibit antipromoter effect on tumors. This effect is of high importance because in the process of carcinogenesis the stage of tumor promotion is reversible, making it an optimal stage for therapy application [36].

On a model of contact hypersensitivity induced in mice by topical or systemic administration of 2,4-dinitrofluorobenzen it was observed that the proanthocyanidins have a protective effect on the immunosuppression induced by UVB. IL-12 and IL-10 are involved in this process. They have an immunosuppressive effect; their level is decreased decrease in the irradiated skin and in the drainage lymphatic nodes after the administration of proanthocyanides (should be edited) [24].

Trans-resveratrol (trans-3, 4′, 5-trihidroxistilbene) is a chemoprotective agent found in red wine and grape. It is responsible for the antitumor effect in different models of carcinogenesis [37]. Tested on SKH-1 mice, resveratrol exerts its effects by modulating the function of survivin, a protein that inhibits apoptosis [1]. The expression of survivin in tumors, especially in melanoma, is associated with cellular proliferation and angiogenesis [38], with an increase of tumor aggressiveness and negative effect on patients' survival rate [1]. For this reason, the inhibition of survivin by therapy is beneficial in advanced and recurrent cases of malignancy and in acute UVB irradiation.

Ursolic acid. Ursolic acid is a triterpenoid pentacyclic compound isolated from flowers (*Calluna vulgaris*) [39] or fruits (apples, plums), with an antiproliferative and cytotoxic effect on different cell lines (multiple mieloma, leukemia, osteosarcoma, mammary carcinoma, lung, pancreatic and skin carcinoma etc) [40]. This compound mainly works by inducing the apoptosis of tumor cells.

The ursolic acid stimulates the activity of caspase-3 [41], reduces the activity of COX-2, interferes with enzymes that play a role in the DNA synthesis, it inhibits the activity of lipooxygenasis, the activation of STAT3, the activation of c-Src, Janus 1, Janus 2 kinases and of the kinases regulated by extra-cellular signal (ERKs) [42, 43]. Also, ursolic acid enhances the apoptotic effect of the antitumor agents used in therapy, and has an anti-mutagen, anti-invasive and antiviral effect.

Some studies reveal the potent inhibitory effect of this compound on epidermoid A431 carcinoma. The ursolic acid reduces the tumor cells growth in a dose-dependent manner by regulating the activity of tyrosine kinase. The modulation of the signal pathways involved in carcinogenesis with the help of the ursolic acid makes this product an attractive option for chemoprevention/chemotherapy [44, 41].

Silibinin. Silibinin, a natural flavonoid used in the whole world as a dietetic supplement due to its photoprotective properties, was brought into view the scientific world because of its protective effect in the photoinduced lesions and in photocarcinogenesis. These effects were discovered by topical and oral administration of this compound [45]. Administering as a part of the diet inhibits the DNA damage and/or stimulates DNA repair, inhibits the proliferation of epidermis cells by inducing the expression of p53 and p21/cip 1 in these cells. The p21 protein binds the proliferating cell nuclear antigen (PCNA) and inhibits its function in DNA replication. Superficial application reduces the formation of thymine dimers immediately after irradiation, not as much due to the sunscreen effect as by interacting at a molecular level in the epidermis [46].

Extract of Uncaria tomentosa. The watery extract of *Uncaria tomentosa* (C-Med-100 or AC-11) increases the reparation of the CPD formed after UVB irradiation. This extract manifests its effect by the reparation of excised bases and also by its antioxidant effect, which leads to the reduction of 8-hydroxyguanine formation, and also by the breakage of the DNA chains. After the extract was administered through gavages to rats in 8 doses each of 40 mg/kg or 80 mg/kg of AC-11, after the rats were irradiated with 12 Gy for 3 h, a complete repair of the DNA strands was observed using both doses [47]. The mechanism by which this compound exerts its effect is still not well understood. It was observed that *Uncaria tomentosa* extract reduces the erythema and the formation of blisters post UV exposure [21].

T4 endonucleases V. T4 endonuclease V (Dimericine) is an enzyme recently synthetised in bacteria

and used in liposome with a protective purpose. It manifests its effect by removing the DNA dimers, especially the cyclobutane pyrimidine, restoring the function of the *p53* gene and by this exerting a protective effect over a long time period. It was used in patients with xeroderma pigmentosum and in patients after transplants to prevent the risk of cancer.

In a clinical trial, it was observed that T4 endonuclease V reduced the incidence of basocellular cancer by 30% and of actinic keratosis by 68% [21]. Its effect on actinic keratosis was noticed after 3 months of treatment, suggesting that T4 endonuclease V compound intervenes in the DNA repair process, influencing both on the promotion and the progression of the tumor. Upon superficial application, this compound is more effective than the usual photoprotective products, because it can be used after the UV irradiation and even after sun burns [48].

The Polypodium leucotomos extract. The *Polypodium leucotomos* extract derived from a plant found in Central America is used in Spain as an oral supplement in patients with arthritis and inflammatory skin disorders (psoriasis) due to its anti-inflammatory properties. It manifests its effect by scavenging the superoxide anion, the singlet oxygen, the lipid peroxides and hydroxyl radical. It offers protection after PUVA therapy for vitiligo, it inhibits the formation of erythema and of CPD, and it holds the Langerhans' cells in the skin [49]. The extract decreases the oxidative stress and stimulate DNA repair.

CHEMOPREVENTION BY MODULATION OF THE SIGNALLING PATHWAYS

The UV irradiation activates a few signalling pathways, especially those involving the signalling transmission from the nucleus to the plasma membrane. These pathways are involved in photoageing, in promoting the tumor growth and invasion, in the survival and proliferation of the cells, and in different DNA lesions. The polyphenols interfere with some signal transduction pathways: p53, growth factors, molecules that regulate the cellular cycle, such as mitogen activated protein kinases (MAPKs), NF-kB, AP-1, phosphatidylinositol 3-kinase and p70 S6-K.

Polyphenols and apoptosis, p53 and cell cycle regulatory molecules. By apoptosis the unwanted or damaged cells are eliminated from the system. Thus, the induction of tumor cells apoptosis could be considered as a protective mechanism against development and progression of cancer. Ahmad *et al.* [50] performed the first studies regarding the role of EGCG in the apoptosis of tumor cells in 1997. They observed that EGCG protects the normal cells by reducing the number of keratinocytes that were sunburned [14, 50]. Other scientific groups working on different cell lines (skin, colon, lung, pancreas, and prostate) confirmed these results [51]. EGCG stimulated apoptosis in precancer lesions (papillomas) and invasive squamous carcinoma [52]. The differentiated effect of EGCG on benign and malignant keratinocytes partially explains its chemoprotective effect in photocarcinogenesis. Although EGCG influences on more than one factor associated with the progression of the cellular cycle, it seems that the primary event is the inhibition of cycline dependent kinases, thereby leading to the induction of negative regulators.

To maintain the integrity of the healthy cells after DNA damage, some cellular responses are activated by transcriptional activation of p53, p21 and Bcl-2 family proteins: the scavenging of the damaged DNA, a delay in the cellular cycle progression and DNA repair [23]. The induction of p53 expression after the DNA damage is associated with an increase in apoptosis of the severely damaged cells. Some studies showed that oral administration of green tea in nude SKH1 mice increased the number of p53 and p21 positive cells in epidermis after irradiation [5, 23]. In addition, the expression of cycline D1 and the retinoblastoma protein phosphorylation were decreased. It was observed that polyphenols induced nuclear condensation, the activation of caspase 3 and the cleavage of poly (ADP)-ribose polymerase. It determines the oligomerization of Bax and the depolarization of the mitochondrial membrane freeing the cytochrome c into the cytosol. These findings are supported by the fact that adding catalase to the cellular system prevents the apoptosis generated by EGCG [5]. Babli *et al.* [53] have shown that treatment with different concentrations of theaflavins and thearubigins from black tea on A375 cells resulted in reduction of Bcl-2 protein expression, whereas increased the Bax expression. The increased ratio of Bax/Bcl-2 proteins may be responsible for the induction of apoptosis in these cells [53].

Polyphenols and MAPKs. MAPK family consist of the extracellular signalling regulatory kinases (ERKs), c-Jun N terminal kinases/stress-activated kinases (JNKs/SAPKs) and p38MAPK proteins. MAPKs are important regulators of the activator protein-1 (AP-1) and nuclear NF-kB transcription factors [23]. The treatment of normal human keratinocytes with EGCG inhibits UV-induced phosphorylation of the MAPK proteins through inhibiton of UV-mediated oxidative stress [5]. The first observations regarding this effect were made in studies *in vitro* on epidermis microsomes from irradiated mice, which were pre-treated with polyphenols. Polyphenols were shown to inhibit the lipid peroxidation and oxidation of proteins [23], inhibiting the glutathione reduction and the decrease in antioxidant enzymes (catalase and glutathion peroxidise) activity [11]. It was shown that polyphenols reduce the DNA damage mediated by the hydroxyl radicals by a mechanism of transfer of electrons from the catechin to the DNA radicals [54]. Applied on the skin of volunteers before they were exposed to four minimum erythema doses, polyphenols significantly reduced the production of hydrogen peroxide and nitric oxide, and also reduced the lipid peroxidation in dermis and epidermis after UVB exposure [11].

Polyphenols and NF-kB. The UV radiation is a potent stimulus for the NF-kB activation. NF- kB is

a transcription factor that belongs to the Rel family. It regulates the expression of genes involved in inflammation, immunity, cellular cycle progression, apoptosis and oncogenesis [55]. NF-kB is sequestered in the cytoplasm in an inactive form due to the interaction with IkB. When IkB is phosphorylated by the IkB kinases (IKK), NF-kB is released and translocated to the nucleus [56]. The activation of NF-kB increases the expression of some pro-inflammatory cytokines and COX-2 and iNOS [24]. Many of these genes are over-expressed in cancers, including the cutaneous ones, and the inhibition of NF-kB with proantocyanidines reduces their expression. EGCG more effectively inhibited NF-kB activation mediated by TNFα on human epidermis carcinoma cells A431 than on normal human keratinocytes [57]. Moreover, EGCG inhibited the degradation and phosphorylation of IkBα, and the activation UV-mediated of IKKα in normal human keratinocytes in a time- and dose-dependent manner [23, 56].

Polyphenols and AP-1. There is an increasing amount of data that suggests the implication of the transcription factor AP-1 in proliferation and survival because of its ability to regulate the expression and the function of some cellular cycle regulatory proteins, such as cycline D1, p53, p21, p19 [23]. The treatment of human keratinocytes HaKaT with EGCG inhibited the UV-induced expression of c-fos, part of AP-1 heterodimer [58]. Chen and Bowden [58] demonstrated that the activation of p38MAPK and ERK is necessary for UVB-induced c-fos expression in HaKaT cells.

Polyphenols, phosphatidylinositol-3-kinase/Akt and p70 S6-K. Phosphatidylinositol-3-kinase (PI3K) and its derived effector Akt/PKB have a crucial role in protein synthesis, apoptosis, cellular growth and mobility [23]. The UVB activates the epidermal growth factor's receptor, which initiates the phosphorylation of Akt. Nomura *et al.* [59] demonstrated that EGCG inhibits the activation of PI3K and UVB induced Akt phosphorylation in mice's epidermis cells, thus blocking the activation UVB-induced of p70 S6-K.

Polyphenols and the proteasome activation. Some studies demonstrated that the proteasome 20S is targeted by EGCG [5]. Proteasome 20S is responsible for p53, p21, $p27^{kip1}$, IkBα, and Bax degradation. *In vitro* experiments showed that ECG and EGCG inhibited the catalytic activity of the 20S complex and intervened in the accumulation of $p27^{kip1}$ and IkBα, and by this induced cell cyle arrest in G1 phase [60].

Polyphenols and COX-2. It was found that cyclooxygenase-2 (COX-2) has an inadequate activity in cancer. COX-2 is an enzyme, which expression is induced by many factors: cytokines, growth factors and tumor promoters. EGCG in concentration of 100 μmols/L inhibited the expression of mitogen-stimulated COX-2 in the prostate androgen-sensitive and androgen-insensitive tumor cells [61].

Polyphenols and the insulin-like growth factor. Insulin-like growth factor (IGF) is an important growth factor involved in maintaining of the normal functions of the cell. The binding of free IGF and IGF-1 leads to intramolecular auto-phosphorylation of the receptor and to the phosphorylation of the specific targets. This is followed by the activation of the PI3K/Akt and Ras/MAPK signalling pathways. Polyphenols substantially reduced the IGF-1 levels and increased the binding protein-3 level in TRAMP mice [5].

Polyphenols and epidermal growth factor receptor (EGFR). The epidermal growth factor receptor (EGFR) is a membrane glycoprotein with three domains: an extracellular, transmembrane and intracellular with tyrosine kinase intrinsic activity. The overexpression of EGFR induces a neoplasic cellular phenotype. The administration of EGCG (10–20 μg/ml) inhibits the activation of EGFR and other signalling pathways in colon tumor cells [5]. EGCG binds to the laminin receptor, expressed in many tumors, in this way exerting its anti-cancer activity [62]. These findings open the door for new studies, which will decipher the mechanisms involved in cutaneous tumorigenesis.

Polyphenols and angiogenesis. Tumor growth requires a continuous and supplementary supply of nutrients and oxygen. To ensure these nutrients, the tumors create new blood vessels. It was recently observed that EGCG reduces the phosphorylation of the VEGF receptor and induces apoptosis in chronic lymphocyte leukaemia [5]. Also, superficial application of EGCG significantly inhibits UVB-induced tumor growth. The inhibition of tumor growth was associated with the reduction of the expression and activity of MMP-2 and -9, which are the crucial factors in tumor invasion and metastasis [36]. Studies demonstrated that EGCG influences the activity of MMPs, both directly and indirectly. The administration of polyphenols 0.1% in the drinking water markedly inhibited the activity of MMP-2 and -9 in the TRAMP mice with prostate cancer [5]. EGCG also inhibits the expression of VEGF in photo-induced tumors and the expression of CD31 on the surface of endothelial vascular cells [36].

CONCLUSIONS

UV radiation has multiple effects on the skin, including sunburn and premature aging, DNA mutations, release of immunomodulatory cytokines, release of reactive oxygen species and alteration of skin Langerhans' cells. The combination of these events can lead to the cancer development. The reviewed natural products are potential candidates for the development of chemopreventive and chemotherapeutic antitumor agents. Understanding the molecular mechanisms of their action and effects on cellular signaling processes as well as their structure-activity relationships is necessary for the generation of new more effective derivatives.

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