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Use of Polyphenolic Compounds in Dermatologic Oncology

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Abstract

Polyphenols are a widely used class of compounds in dermatology. While phenol itself, the most basic member of the phenol family, is chemically synthesized, most polyphenolic compounds are found in plants and form part of their defense mechanism against decomposition. Polyphenolic compounds, which include phenolic acids, flavonoids, stilbenes, and lignans, play an integral role in preventing the attack on plants by bacteria and fungi, as well as serving as cross-links in plant polymers. There is also mounting evidence that polyphenolic compounds play an important role in human health as well. One of the most important benefits, which puts them in the spotlight of current studies, is their antitumor profile. Some of these polyphenolic compounds have already presented promising results in either in vitro or in vivo studies for non-melanoma skin cancer and melanoma. These compounds act on several biomolecular pathways including cell division cycle arrest, autophagy, and apoptosis. Indeed, such natural compounds may be of potential for both preventive and therapeutic fields of cancer. This review evaluates the existing scientific literature in order to provide support for new research opportunities using polyphenolic compounds in oncodermatology.

1. Introduction

Polyphenolic compounds are found in numerous plants and vegetables and are part of the human diet [1]. Both plants and fungi (mushrooms) are considered among the most important sources of polyphenolic compounds [2]. Polyphenolic compounds are rapidly metabolized in the human body [3–5], circulating as their conjugated forms such as glucuronide, methylated, and sulphated derivatives [1]. Several polyphenolic compounds have a very well known anti-angiogenic profile [6–8], mainly because of their anti-inflammatory, antimicrobial, antitumor, and antioxidant properties [1, 9–11]. Rapid metabolism and poor absorption have limited the therapeutic potential of polyphenolic compounds up to now.

Phenol, a mono-phenyl ring bonded to a hydroxyl group, is the most important representative of the phenolic compounds. It is considered a kerato-coagulant agent at a

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Compliance with Ethical Standards

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concentration of 88 % [12, 13], with similar effects to a 70 % trichloroacetic acid (TCA) peel [12], or CO₂ non-fractional laser [13]. Nonetheless, its skin penetration can be decreased by alcohol; for example, applying poly-ethylene glycol 400, or 70 % isopropanol diluted with water [14]. Skin treated with topical application of phenol presents with immediate vascular coagulation, keratin epidermal coagulation, and injury to the upper reticular dermis, which is why it is commonly used for deep-tissue peels in cosmetic dermatology [12]. In addition, phenol decreases melanogenesis [15], as a peroxidase inhibitor, reducing the polymerization of melanogenic intermediates [16, 17]. Furthermore, it decreases melanocyte proliferation [17].

Although phenol has not been used specifically against skin cancer, many other polyphenolic compounds show potential in skin cancer therapy. We started our review of the literature at 1973, exploring PubMed manuscripts that had as descriptors the name of the polyphenolic compound in 'Title', and the words 'skin cancer', 'skin', 'cancer', 'dermatology', 'cutaneous', 'neoplasia', and 'tumor' in 'Title/Abstract'. Moreover, we also used some iconic books and international standards as additional references. Based on the results obtained from this search, we explored polyphenolic compounds in detail, evaluating their merits as possible agents in dermatologic oncology.

All polyphenolic compounds studied in this manuscript are described in alphabetical order and their chemical structures and characteristics are summarized in Fig. 1 [18–25]. A summary of mechanisms of action of these polyphenolic compounds can be found either in Table 1 or Fig. 2, which are complementary to each other.

2. Curcumin

Curcumin is a natural plant polyphenol pigment found in *Curcuma longa* [26]. Obtained from the turmeric rhizome, curcumin is widely used in traditional Chinese medicine [27] as an anti-inflammatory, antioxidant, anticancer, antimicrobial, cosmetic depigmenting agent and wound healing agent [28–31], and for the treatment of psoriasis [32–34].

However, curcumin has poor systemic bioavailability when administered orally [35]; it is poorly insoluble in water [36], and suffers first-pass metabolism in the liver [37–39]. This has stimulated its use via transdermal application [40], since topical use of curcumin is considered as effective as systemic use [40, 41], including when dissolved into modern topical vehicles [41, 42]. Modern topical vehicles can protect curcumin against ultraviolet B (UVB) degradation; these novel topical formulations include ethyl cellulose and/or methyl cellulose nanoparticles [43, 44], β -cyclodextrin-curcumin-nanoparticle complexes [41], curcumin-loaded soybean phospholipid liposomes [42], curcumin-encapsulated chitosan-bioglass [45], lipid vesicle-propylene glycol liposomes [46], and curcumin-loaded chitin nanogels [47].

Curcumin and some of its derivatives, such as 1,3-bis-(2-substituted-phenyl)-propane-1,3-dione [48], are promising for therapy against non-melanoma skin cancer. In animal models, topical and/or systemic curcumin reduced the size of human squamous cell carcinoma SRB12-p9 by inhibiting phosphorylated protein kinase B (p-AKT), protein S6 (pS6),

phosphorylation of eukaryotic translation initiation factor 4E binding protein-1 (p-4EBP1), phosphorylated-signal transducer and activator of transcription 3 (p-STAT-3), and phosphorylated-extracellular signal-regulated kinase 1/2 (p-ERK1/2) in vitro, as well as p-STAT-3 and p-ERK1/2 activation of p-ERK and pS6 in vivo [48, 49]. These actions can be enhanced because curcumin is a selective and non-competitive phosphorylase-kinase agent, helping to decrease 12-*O*-tetradecanoylphorbol-13-acetate-induced protein kinase C translocation [50–52] and because curcumin inhibits the insulin growth factor-1 (IGF-1)-carcinogenic signaling as well [53]. The effect of curcumin on signal transducer and activator of transcription 3 (STAT-3) seems to be important for preventing growth of A341 melanoma cells as well [26] (Table 1; Fig. 2).

In an animal study, curcumin (10 mmol/200 mL acetone) was topically applied 30 minutes prior to UVB (180 mJ/cm²) irradiation [54]: curcumin decreased UVB-induced thymine dimer-positive cells, expression of proliferation cell nuclear antigen (PCNA), terminal deoxynucleotidyl transferase-mediated 2'-deoxyuridine 5'-triphosphate (dUTP) nick end labeling, apoptotic sunburn cells, and increased protein p53 (p53) and cyclin-dependent kinase inhibitor 1A (Cip/p21)-positive cells. Such findings were associated with inhibition of prostaglandin E2 (PGE-2) and nitric oxide (NO) [54], as well as the cyclooxygenase-2 (COX-2) expression through nuclear factor-kappa B (NF-κB) [54, 55]. By blocking NF-κB, curcumin inhibits T-cell response, and both epidermal and fibroblast proliferation [50] (Table 1).

Under ultraviolet A (UVA) or visible light exposure, curcumin inhibits keratinocyte proliferation, enhances the release of cytochrome C, and inhibits NF-κB [56]. Furthermore, under UVA radiation, curcumin inhibits induction of reactive oxygen species (ROS) and toxic membrane UVA-induced damage, preventing increased production of apoptotic bodies and activated caspases, while inhibiting protein kinase B (AKT), ERK1/2, and epidermal growth factor receptor (EGF-r) [56] (Table 1).

In melanoma cell studies, curcumin and analogs [57, 58] reduce proliferation, migration, and invasion of melanoma and induce apoptosis [59–62]. Curcumin's lipophilic profile has encouraged its use in transdermal devices [63]; moreover, when curcumin is used topically, visible light enhances the anti-melanoma effects of curcumin, implying a potential photodynamic effect [64].

When curcumin is administered intravenously concurrently with an anti-melanoma vaccine, it boosts in vivo cytotoxic T-lymphocyte response, downregulates levels of some immunosuppressive factors, such as myeloid-derived suppressor cells, regulatory T cells, interleukin-6 (IL-6) and chemokine ligand-2, and increases levels of some proinflammatory cytokines [65], including tumor necrosis factor-α (TNF-α) [65, 66] and interferon gamma (IFN-γ) [65], as well as resulting in an elevation of the cytotoxic T cell CD8-positive (CD8+ T-cell) population [65, 66] (Table 1).

Curcumin leads to apoptosis of melanoma in a mitochondrial-caspase-dependent pathway [67, 68], since curcumin is also associated with such organelle permeability transition pore opening [69]. Such an apoptotic scenario involves the activation of macrophage stimulating

1 protein (MST-1), which activates Jun amino-terminal kinases (JNK) and forkhead box protein O3 (FOXO3) nuclear translocation [70], as well as downregulation of NF- κ B [71–73]. Furthermore, decreased pulmonary tumor formation has been seen in a murine model of experimental metastatic melanoma using orally administered curcumin, which was associated with significantly decreased expression of metalloproteinases [74, 75]; this mechanism could be one of the reasons why curcumin sensitizes melanoma cells to tamoxifen [76] (Table 1; Fig. 2).

3. Ellagic Acid

Ellagic acid is found in different fruits such as berries, pomegranates, and nuts, and is a popular dietary supplement [77]. Experiments have already shown that ellagic acid has antifibrotic, antiproliferative, antibiofilm, and antitumorigenic properties [77–84]. Ellagic acid is a potent polyphenolic agent, despite its poor solubility and permeability [85].

Ellagic acid is metabolized by gut microbiota to yield urolithins [86–88]. There are three human phenotypes for urolithin production: phenotype A, in 25–85 % of the population that produces only urolithin A conjugates; phenotype B, in 10–50 % of the population that produces isourolithin A and/or urolithin B in addition to urolithin A and is associated with gut microbial imbalance (i.e., dysbiosis in which there is also an increased risk of chronic illness such as metabolic syndrome) or colorectal cancer; and phenotype 0, in 5–25 % of the population in which no urolithins are observed [89]. The systemic anti-inflammatory role of ellagic acid [90–92] seems to stem mainly from its metabolite, urolithin-A; it inhibits activation of NF- κ B and mitogen-activated protein kinase (MAPK), downregulates COX-2 and membrane-associated PGE synthase 1 (mPGES-1) expression, reducing PGE-2 production [92].

Potential dermatologic uses of ellagic acid are suggested by its in vitro anti-proliferative effect against melanoma cells [93, 94]. Ellagic acid promotes gap 1 (G1) cell cycle arrest, increases apoptosis, and decreases synthesis of IL-1 β , IL-8, and NF- κ B [94]. Topical [95] and systemic use of ellagic acid in animals [96, 97] inhibits epidermal tumor generation caused by some environmental tumorigenesis chemicals such as 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA) [95], 3-methylcholantrene [96, 97], or benzo[a]-pyrene and ($\pm$)-7 β , 8 α -dihydroxy-9 α ,10 α -epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene [98]. Ellagic acid also acts on oral carcinoma cells [99] (Table 1).

Ellagic acid reduces in vitro UVB-induced expression of IL-1 β [100], IL-6 [100, 101], IL-8, monocyte chemoattractant protein-1 (MCP-1), and TNF- α [101], increases anti-UVB protective IL-10 expression [101], and inhibits intercellular adhesion molecule-1 (ICAM-1)-UVB-dependent expression [100] in keratinocytes. Ellagic acid also helps UVB-exposed fibroblast to block metalloproteinase (MMP) secretion and collagen degradation, leading to less wrinkles and thickness [100]. A 4-week oral supplementation with 100–200 mg/day of ellagic acid produced a slight increase in the minimum erythema dose value caused by UV exposure [102], since it is shown to inhibit tyrosinase activity [103], which means it may also be useful as an anti-melasma agent [104] (Table 1).

Finally, ellagic acid-treated HaCaT cells show increased viability and decreased ROS generation after UVA exposure, with a higher expression of superoxide dismutase, and hemeoxygenase 1. These actions may prevent deoxyribonucleic acid (DNA) fragmentation, decrease mitochondrial impairment, activate caspase-3, prevent endoplasmatic reticulum stress, and deregulate B-cell lymphoma 2(BCL2)/BCL2-associated X protein (Bcl/Bax) pathway [105] (Table 1; Fig. 2).

4. Epicatechin Gallate

Epicatechin gallate, or (2)2-epigallocatechin-3-gallate, is a catechin derived from *Camellia sinensis* [106] and has anti-inflammatory, antioxidative, antimutagenic, anticarcinogenic, apoptotic [106–110], and wound-healing properties [111–113], among others. Nonetheless, paradoxically, at high doses, epicatechin gallate may stimulate hypoxia-inducible factor 1- α (HIF1- α) and tumor cell survival [114].

Green tea is one of the most important sources of epicatechin gallate, as well as for other catechins, such as (2)2-epicatechin gallate (ECG), (2)2-epicatechin (EC), and (2)2-epigallocatechin [106]. In fact, epicatechin gallate is the most abundant polyphenolic compound found in green tea [107, 108], albeit final biological green tea effects likely result from a combination of catechins [115].

Epicatechin gallate protects HaCaT keratinocytes against UVB- and UVA-induced oxidative damage [116–119]. A potential mechanism is that epicatechin gallate suppresses UVA-mediated release of labile iron, since it contributes to lysosomal protection, avoids protease release, and blocks ferritin degradation [117]. This prevents iron-mediated fibroblast and keratinocyte apoptosis [120]. In head and neck squamous cell carcinoma, epicatechin gallate leads to suppression of cyclin D1 [121], induces caspase-3 activity [121, 122], and inhibits ribonuclease-A by copper complexes [123]. However, further studies need to be done with epicatechin gallate and melanoma (Table 1; Fig. 2).

5. Eugenol

Eugenol, also named 4-allyl-2-methoxyphenol, a component of cloves or *Syzygium aromaticum* [124], is a polyphenolic compound also obtained from other aromatic plants, such as basil, cinnamon, and bay leaves [125, 126]. This polyphenolic compound has anti-fungal activity [127]. Eugenol can be used in perfumes and fragrance-based creams [128, 129]; however, it is considered an important sensitizer [127–130].

Some studies have shown that eugenol has anti-neoplastic activity, since eugenol suppresses mutagenicity caused by furylfuramide, 4-nitroquinoline N-oxide, and aflatoxin B in *Salmonella typhimurium* [131–135]; additionally, it modulates enzymatic detoxification by inhibiting 7,12-dimethyl-benz[a]anthracene (DMBA)-induced DNA damage [133, 134]. Furthermore, when mice receive oral supplementation with eugenol, it restricts croton oil-induced skin carcinogenesis through attenuation of v-myc avian myelocytomatosis viral oncogene homolog (c-Myc), human-‘rat sarcoma’ protein family (H-Ras), and modification of some p53-associated gene expression [136] (Table 1; Fig. 2).

6. Honokiol

Honokiol is a bioactive, biphenolic constituent found in the leaves and bark of *Magnolia officinalis* and other plants of the genus *Magnolia* [137–139]. Honokiol use comes from the traditional Japanese medicine ‘Saiboku-to’, which has been used for a long time as an anxiolytic, antithrombotic, antidepressant, and antibacterial compound [140]. Moreover, honokiol has also demonstrated antibacterial, anti-inflammatory, antifungicidal, antioxidative, anticarcinogenic [139–147], and antiviral activities [148–151], besides ameliorating pre-existing cardiac hypertrophy [152].

At a glance, as an anticarcinogenic agent in melanoma, honokiol inhibits proliferation, viability, and clonogenicity, induces autophagy, inhibits melanosphere formation, and controls cell size in a dose-dependent manner [153, 154]. However, several other additional mechanisms of action of honokiol have been described.

First, honokiol increases cytosolic cytochrome C in cytoplasm, resulting in increased caspase activity, and increased mitochondrial depolarization [137, 138, 153, 155–157]. Second, honokiol directly inhibits ROS-dependent NF- κ B via scavenging superoxide and peroxy radicals [158]. Third, honokiol antagonizes AKT via increased phosphorylation/activation of adenosine monophosphate kinase (AMPK). Fourth, honokiol decreases the cellular adenosine triphosphate (ATP) pool in a dose- and time-dependent manner [153]. Fifth, honokiol targets Notch signaling [154, 156], a kind of single transmembrane receptor family, by suppressing the expression of astrocyte and endothelial cell expression of TNF- α converting enzyme (TACE or ADAM 17) [154], and γ -secretase complex proteins in cells [154, 156], reducing stem cell markers such as cytotoxic T cell CD271-positive (CD271), cytotoxic T cell CD166-positive (CD166), Jumonji/ARID Domain-Containing Protein 1B (Jarid1b), and ATP-binding cassette sub-family B member 5 (ABCB5), thus reducing the cleaved Notch-2 expression, which is involved in stem cell self-renewal [154] (Table 1; Fig. 2).

In vivo experiments also support the in vitro activity of honokiol against both melanoma and non-melanoma skin cancer [137, 138, 157, 158]. Honokiol demonstrates a dose-dependent effect with topical usage, reducing volume and tumor growth, either before or after UVB radiation [138, 157], possibly through inhibition of COX-2, PGE-2, PCNA, and pro-inflammatory cytokines (TNF- α , IL-1 β , and IL-6), further inhibiting cyclins D1, D2, and E, and phosphatidylinositol 3-kinase (which decreases phosphorylation of AKT at Ser473) and of associated cyclin-dependent kinases (CDK) 2, CDK4, and CDK6, and consequently upregulating Cip/p21 and CDK inhibitor 1B (Kip/p27) expression [137] (Table 1).

In non-melanoma skin cancer, honokiol downregulates the expression of cyclin D1, D2, CDK2, CDK4, and CDK6, upregulating the expression of the CDK inhibitor proteins p21 and p27 in human epidermoid squamous carcinoma, inducing apoptosis and DNA fragmentation, gap 0/gap1 (G0/G1) cell cycle arrest, and decreasing the percentage of cells in the synthesis (S) and gap2/mitosis (G2/M) phases [157]. The activity of honokiol against skin cancer can be increased when associated with α -santalol—an active component of sandalwood oil—and magnolol [159] (Table 1).

Honokiol also inhibits protein Ki-67 expression and increases terminal deoxyuridine triphosphate nick end labeling (TUNEL)-positive cells, by inducing mitochondria-dependent and death receptor-mediated apoptosis, secondary to inhibition of EGF-r/STAT-3 signaling and downregulation of STAT-3 target genes, helping paclitaxel to improve its chemotherapy capability [160]. Additionally, honokiol inhibits other EGF-r signaling, as a downstream inhibition of MAPK, AKT, and expression of STAT-3 target genes, such as B-cell lymphoma-extra large (Bcl-XL) and cyclin D1 [161]. These two main actions synergize with paclitaxel and erlotinib chemotherapy [160, 161] (Table 1; Fig. 2).

Finally, honokiol induces endoplasmatic reticulum stress and unfolded protein response in neuroectodermal tumor cells lines, such as melanoma, glioblastoma, neuroblastoma, and angiosarcoma, after it binds and activates glucose regulated protein 78 (grp78) [159].

7. Resveratrol

Resveratrol is a polyphenolic compound found in grapes, nuts, and berries [162] that increases mitochondrial biogenesis, acting as an anti-inflammatory, anti-diabetic, and anti-cancer compound [163], skin-depigmenting agent [162, 164, 165], anti-psoriatic [166], and wound-healing agent [167], among other properties.

In normal keratinocytes, resveratrol inhibits their proliferation [164] by downregulating aquaporin 3 via a sirtuin-1/aryl hydrocarbon receptor nuclear translocator/extracellular signal-regulated kinase (SIRT1/ARN/ERK)-dependent pathway [165], being cytotoxic at high concentrations [164]. Moreover, it has anti-inflammatory effects on macrophage, adipocyte, cultured adipocytes, and adipose tissue [162], as well as down-regulating tyrosinase [168] on melanocytes [166–171].

Using Franz vertical diffusion with porcine ear skin as a biological membrane, resveratrol was shown to improve sunscreen safety when associated with beta-carotene, by reducing by 63 % the delivery of octocrylene, octyl methoxycinnamate, avobenzone, and bemotrizinole into the stratum corneum and viable epidermis [172]. New delivery systems can enhance its epidermal penetration [173–178].

Resveratrol acts as a potent antioxidant. In a cigarette-based in vitro keratinocyte model, resveratrol shows an important antioxidative action [179, 180], stimulating the nuclear factor-like 2 (Nrf2) pathway by decreasing the Nrf2 repressor Kelch-like ECH-associated protein 1 (Keap1) protein [181], allowing translocation of Nrf2 to the nucleus, producing glutathione [182–184] and super-oxide dismutase [182], which protects the dermal–epidermal junction in full-thickness reconstructed human skin [183, 184]. In addition, resveratrol stimulates the 5' adenosine monophosphate (AMP)-activated protein kinase/ forkhead box protein O3 (AMPK-FOXO3) cascade [185] and dose-dependently reduces intracellular hydrogen peroxide in human fibroblasts [186]. By decreasing malonaldehyde content in HaCaT cells under UVA irradiation [182], resveratrol may be useful as an alternative approach for non-melanoma skin cancers [187, 188] (Table 1).

In skin squamous cell carcinoma, resveratrol increases apoptosis by upregulating expression of p53 and ERK and downregulating expression of survivin (SVV), the strongest inhibitor of

apoptosis protein (IAP) family members [189]. By downregulating the complex known as the regulatory associated protein of mTOR (RPTOR)-independent companion of mechanistic target of rapamycin (MTOR), or simply RICTOR, which is an mTOR complex 2 (mTORC2) component, resveratrol promotes premature senescence [190]; and by inhibiting autophagy, it enhances apoptosis [191] (Table 1; Fig. 2).

Resveratrol also interacts with the toll-like receptor 4 (TLR-4)-dependent anti-tumor pathway. In this case, resveratrol acts as an antiangiogenic factor, as well as enhancing IFN- γ and IL-12 cell-mediated immune response [192]. Furthermore, resveratrol inhibits phorbol ester-induced expression of COX-2, since resveratrol either blocks I κ B kinase (IKK α) activity (and activation of NF- κ B) [193, 194], or activates MAPK and the activator protein-1 (AP-1) pathway [194, 195] (Table 1).

With regards to using chemical agents as tumor enhancers, topical use of resveratrol before 7,12-dimethyl benz(a)anthracene topical application reduces tumorigenesis in mice, since it increases p53 and Bax expression [196, 197], decreases Bcl-2 and SVV expression [198], releases cytochrome C [191, 196], activates caspases-3 and -9 [196, 197], increases apoptotic protease-activating factor-1 (Apaf-1) [196, 197], and regulates phosphatidylinositol-3-kinase (PI3K)/AKT proteins [196]. All those findings show that resveratrol uses pro-apoptotic mitochondrial pathways [196, 197, 199]. Finally, if chemically induced tumor cells are infected with Epstein-Barr virus, resveratrol acts as an anti-oxidant and pro-cytotoxic chemopreventive agent [200] (Table 1; Fig. 2).

As with topical use [172], a systemic combination of resveratrol with other compounds may be useful in chemo-preventive and therapeutic strategies. When combined with black tea polyphenol, resveratrol decreases the expression of phosphorylated MAPK family proteins, such as ERK1/2, JNK1/2, and protein p38 (p38), increases the total amount of p53 and phospho-p53 (Ser 15) in skin tissue and tumor, and decreases expression of PCNA [198]. These activities enhance the combination with ursolic acid to enhance its anti-cancer effect in skin carcinoma cells [201] (Fig. 2).

Since resveratrol can cause DNA damage to squamous cell carcinoma in the head and neck area [202], causing p53-dependent apoptosis [203], and inhibiting accumulation of hypoxia-inducible factor-1 α and vascular endothelial growth factor (VEGF) expression [204], resveratrol can be used as either a chemopreventive agent [205, 206] or a therapeutic one, improving cytotoxic irradiation-based therapy, by decreasing cyclin B, cyclin D, CDK2, CDK4, and the anti-apoptotic molecule Fas-associated protein with death domain-like IL-1 β -converting enzyme-inhibitory protein (FLIP), Bcl-2, and SVV [178, 207–209]. Resveratrol may also improve the cytotoxicity of 5-fluorouracil [210, 211] (Table 1; Fig. 2).

Resveratrol is also photoprotective against either UVB-or UVA-induced responses in keratinocytes [212]. In a UVB-induced skin cancer mouse model, SVV seems to be decreased in either pre- or post-topical treatment with resveratrol [213, 214]; further, if resveratrol is applied before, it modulates the expression and function of cell cycle regulatory proteins cyclin D1 and D2, as well as CDK2, CDK4 and CDK6, and WAF1/p21, perhaps associated with inhibition of the MAPK pathway [215]. Resveratrol also blocks, in a

dose-dependent manner, the UVB-mediated NF- κ B pathway, through phosphorylation and degradation of I κ B α and activation of IKK α [216]. In association with these findings, resveratrol prolongs cell survival, once it reduces ROS formation, inhibits caspase-8, leads to poly ADP (adenosine diphosphate) ribose polymerase (PARP) cleavage, and induces autophagy [217]. For this reason, it could be useful for preventing UVB-mediated damage [187], and enhancing the response to radiation therapy against inflammatory and premalignant conditions [218]. Furthermore, Resveratrol leads UVA-damaged keratinocytes to apoptosis by producing oxidative stress in mitochondria, which increases the organelle permeability transition pores [219] (Table 1; Fig. 2).

Finally, resveratrol has been shown to be a pro-apoptotic compound against melanoma [219], inducing apoptosis once it induces G1/S cell cycle arrest [27, 220–223], through expression of dihydronicotinamide riboside quinone reductase 2 and p53 [221], upregulation of cyclins A, E, and B1 [223], suppression of STAT-3/ β -catenin-pathway [224], and production of NO, which stimulates p53 and Bax-Bcl2 mitochondrial apoptosis [225, 226]. Subsequently, cytochrome C, and caspase-9 and -3 are released [227, 228]. Furthermore, apurinic/aprimidinic endonuclease-1/redox factor-1 (APE/Ref-1), a protein enrolled in tumorigenesis, is inhibited [226, 229], resulting in a coordinated decrease in AP-1/JunD protein, MMP-1 and inducible NO (iNO) protein levels [226]. It reduces tumor invasiveness by inhibition of α -melanocyte-stimulating hormone (α -MSH) expression [230]. Furthermore, autophagy is also observed through ceramide accumulation and AKT/mTOR inhibition [231] (Table 1; Fig. 2).

As an oral supplementation, resveratrol downregulates and inactivates AKT, an anti-apoptotic protein, reducing primary tumor volume, AKT expression, and the propensity for metastasis in animals [232]. Resveratrol also decreases AMP-activated protein kinase, COX-2, vasodilator-stimulated phosphoprotein [232], VEGF [211, 232] and its VEGF-sensitive HIF1- α , and increases expression of anti-angiogenic factors thrombospondin-1 and p53 [42]. Those anti-angiogenic metastatic pathways inhibit liver melanoma metastasis [233] by inhibiting lipopolysaccharide-induced epithelial-mesenchymal transition of IL-8 [234], VEGF-stimulated NO production, and basic fibroblast growth factor (bFGF)-stimulated COX-2 induction in fibroblasts [235] (Table 1; Fig. 2).

8. Salicylic Acid

Salicylic acid, or ortho-hydroxybenzoic acid, is a beta-hydroxy acid [236]. It is found in the bark of the willow tree, *Salix alba*, and has been used for skin disorders for over 2000 years [237]. Salicylic acid is also described as having keratolytic, bacteriostatic, fungicidal, and photo-protective properties [238].

Under topical use, salicylic acid reduces skin sensitivity in solar-simulated radiation, reducing erythema, DNA damage, and sunburn cell formation [236], increasing cutaneous minimum phototoxic dose and minimum erythema dose prior to UVA [239] and UVB [240] exposures. This explains why salicylic acid interferes with skin cancer development in animal models [241] and treats actinic keratosis, alone and in combination with 0.5 % 5-fluorouracil [242–245].

Salicylic acid is metabolized by tyrosinase [246, 247]. This process seems to be the cause for suppressing the proliferation of B16 and SK-28 human melanoma cells at a plasma-attainable and nontoxic level, probably because it induces the activation of p38 and JNK MAPKs, being synergistic with 1,3-bis(2-chloroethyl)-1-nitrosourea [248] (Fig. 2).

Finally, salicylic acid significantly depletes intracellular glutathione in melanoma cell lines, as well as ROS formation, which suggests that quinone species, intracellular glutathione depletion, and mitochondrial toxicity significantly contribute toward s the selective toxicity of salicylic acid in melanocytic melanoma cells, which is not observed in amelanotic ones [246] (Table 1).

9. Tannic Acid

Penta-*m*-digalloyl-glucose, or simply tannic acid, is a polyphenolic compound found in the bark and fruits of many plants [249], and is formed in animals' bodies as the secondary metabolism of those plants [249–251]. Tannic acid is the main source of the pro-apoptotic agent gallic acid [251], but is considered more potent than ellagic acid [252]. Tannic acid is an antioxidant, anti-inflammatory, and anti-proliferative agent [253–255].

Tannic acid's antioxidant effect [253–255] occurs because it reduces lipid peroxidation, COX-2, inducible nitric oxide synthase (i-NOS), and PCNA expression, increases reduced glutathione, decreases pro-inflammatory cytokines such as IL-6 and NF- κ B, and depletes both hydrogen peroxide and xanthine oxidase [253]. Indeed, it is highly likely that these mechanisms are also important in providing tannic acid's anti-carcinogenic profile.

Tannic acid's important anti-carcinogenic mechanism of action is its capability of strongly inhibiting EGF-r tyrosine kinase [256]. Furthermore, tannic acid acts against topical skin cancer inducers [81, 95, 252, 257–259] such as DMBA plus croton oil-induced skin cancer [249, 258] and TPA [259]. More recent studies have shown that tannic acid prevents UVB-induced cutaneous carcinogenesis [260, 261], because it downregulates IL-18 [260]. The effect of tannic acid on the prevention and/or treatment of melanoma has not been studied yet (Table 1).

10. Conclusion

Polyphenolic compounds are already being used in different areas of dermatology and this manuscript provides a comprehensive review focused on the activity of these compounds in oncodermatology. Phenol itself acts as a physical destructive agent, but the addition of hydroxyl groups and rings results in additional biological properties, including disruption of hydrogen bonding, enhancement of mitochondrial metabolism, blockage of NF- κ B and other effects. On the other hand, natural polyphenolic compounds can be delivered in relatively high concentrations to the skin using optimized formulations, allowing the proposed beneficial effects on cellular signaling to occur, as opposed to systemic delivery, in which these compounds are poorly absorbed and rapidly metabolized.

Given that knowledge of the polyphenolic compounds may be considered essential for practicing dermatologists, we aim to help dermatologists understand the variety of

mechanisms of actions associated with these compounds. In fact, the diverse and distinct mechanisms of actions available provide new opportunities for researchers to explore polyphenolic compounds not only in dermatology but also in oncology. Curcumin, ellagic acid, epicatechin gallate, eugenol, honokiol, resveratrol, salicylic acid and tannic acid act as anti-cancer agents in important pro-neoplastic cell aspects, such as inflammation, autophagy, apoptosis, cell growth, and cell survival. Without doubt, this diversity of actions represents a unique advantage.

Polyphenolic compounds are already used in over-the-counter preparations, prescription drugs, sunscreens, and oral supplements. Increased frequency of the use of polyphenolic compounds in commercial products is expected. We believe that sunscreens are most likely to see an increase in use of polyphenolic compounds. However, it is likely that many other compounds will enter the dermatologic marketplace within the next decade. For instance, currently, there is one FDA-approved product of topical catechins, based on sinecatechins ointment 10 % (Veregen®; PharmaDerm®, a division of Fougere Pharmaceuticals Inc., Princeton, NJ, USA), which is formulated from green tea (*Camellia sinensis*) extracts, for the treatment of external genital warts and perianal warts in patients 18 years and older [262].

Because of the scientific evidence and benefits related to polyphenolic compounds as described in this review, it is considered essential for the practicing dermatologist to understand the variety of mechanisms of action related to these ubiquitous compounds.

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Key Points

Polyphenolic compounds have both current and future potential impact in dermatologic oncology.

We strongly believe that, in addition to non-melanoma skin cancer, melanoma can be targeted by polyphenolic compounds.

These compounds are already in use in both prescription and over-the-counter formulations, but the impact on dermatologic oncology is not yet fully understood.

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Curcumin	Ellagic acid	Epigallocatechin gallate	Eugenol

Number of phenolic rings: 2	Number of phenolic rings: 2	Number of phenolic rings: 3	Number of phenolic rings: 1
Chemical formula: C ₂₁ H ₂₀ O ₆	Chemical formula: C ₁₄ H ₆ O ₈	Chemical formula: C ₂₂ H ₁₈ O ₁₁	Chemical formula: C ₁₀ H ₁₂ O ₂
Molar mass: 368.3799 g/mol	Molar mass: 302.19264 g/mol	Molar mass: 458.37172 g/mol	Molar mass: 164.20108 g/mol
Honokiol	Resveratrol	Salicylic acid	Tannic acid

Number of phenolic rings: 2	Number of phenolic rings: 2	Number of phenolic rings: 1	Number of phenolic rings: 10
Chemical formula: C ₁₈ H ₁₈ O ₂	Chemical formula: C ₁₄ H ₁₂ O ₃	Chemical formula: C ₇ H ₆ O ₃	Chemical formula: C ₇₆ H ₅₂ O ₄₆
Molar mass: 266.33432 g/mol	Molar mass: 228.24328 g/mol	Molar mass: 138.12074 g/mol	Molar mass: 1701.19848 g/mol

Fig. 1.

Chemical overview of the phenolic compounds explored in this manuscript [18–25]

Fig. 2.

Protein-dependent biomolecular pathways changed by some polyphenolic compounds, as a complement to the information in Table 1. *Solid black arrow* indicates physiological stimulation, *solid black line with an end block* indicates physiological blockage, *black dotted arrow* indicates physiological stimulation with intermediate pathways that weren't studied in this manuscript, *black dotted line with an end block* indicates pathway blocked by the polyphenolic compound, *solid green arrow* indicates pathway stimulated by the polyphenolic compound, *solid red arrow* indicates pathway downregulated by the polyphenolic compound, *solid red line with an end block* indicates pathway blocked by the polyphenolic compound, *red dotted line with an end block* indicates physiological block with intermediate pathways that weren't studied in this manuscript. *AKT* protein kinase B (also named PKB), *Bax* Bcl-2-associated X protein, *Bcl-2* B-cell lymphoma 2, *C-myc* v-myc avian myelocytomatosis viral oncogene homolog, *EGF-r* epidermal growth factor receptor, *ERK* extracellular signal-regulated kinase, *iNO* inducible nitric oxide, *JNK* Jun amino-terminal kinases, *MST-1* macrophage stimulating 1 protein, *mTOR* mechanistic target of rapamycin, *NO* nitric oxide, *p-4EBP1* phosphorylation of eukaryotic translation initiation factor 4E binding protein-1, *p21* protein p21, *p38* protein p38, *p53* protein p53, *pS6* protein S6, *Ras* 'rat sarcoma' protein family, *STAT-3* signal transducer and activator of transcription

Table 1

Chemically dependent biomolecular pathways changed by some polyphenolic compounds, as a complement to Fig. 2

Name of the polyphenolic compound	Anti-oncogenic mechanisms of action in skin cancer
Curcumin	Inhibition of p-4EBP1 [48, 49] Decreases 12-O-tetradecanoylphorbol-13-acetate-induced protein kinase C translocation and inhibits IGF-1-carcinogenic signaling [48–53] Decreasing of UVB-induced thymine dimer-positive cells, expression of PCNA, terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling, and apoptotic sunburn cells [54] Inhibition of PGE-2, NO, and COX-2 NF- κ B [54–56] Inhibition of ROS production and toxic membrane UVA-induced damage [56] Stimulates cytotoxic T-lymphocyte response downregulating myeloid-derived suppressor cells, regulatory T cells, and IL-6 and chemokine ligand-2 [65] Increases TNF- α , IFN- γ , and CD8+ T-cell population [65, 66]
Ellagic acid	Promotion of G1 cell cycle arrest, increasing of apoptosis and decreasing of IL-1 β , IL-6, IL-8, IL-10, and NF- κ B [94, 100, 101] Reduction of MCP-1, and TNF- α [101] Expression of ICAM-1-UVB-dependent [100] Expression of superoxide dismutase and heme-oxygenase 1 [105] Inhibition of apoptosis: prevention of DNA fragmentation and decreasing of both mitochondria impairment and endoplasmatic reticulum stress [105]
Epicatechin gallate	Suppression of UVA-mediated release of labile iron [117] Suppression of cyclin D1 [121] Induction of caspase-3 activity [121, 122] Inhibition of ribonuclease-A by copper complexes [123]
Honokiol	Induces cycle G0/G1 cell arrest [157] Inhibition of ROS-dependent NF- κ B [158] Decreasing of ATP pool [153] Decreasing of Notch signaling [154, 156] Inhibition on the UVB-induced expression of COX-2, PGE2, proliferating cell nuclear antigen, and some pro-inflammatory cytokines [137] Inhibition of Ki-67 expression and an increase in TUNEL-positive cells [160]
Resveratrol	Stimulates Nrf2 [181–184] Produces glutathione and superoxide dismutase, decreases malonaldehyde content [182–184] Stimulates AMPK-FOXO3 [185] Downregulates Rictor [190] Stimulation of TLR-4 pathway [192] Blocking of I κ B kinase activity [193, 194] Activation of MAPKs and AP-1 pathway [194, 195] Increases Apaf-1 [196, 197] Decreases the expression of extracellular signal-regulated kinase 1/2 and p38 [198] Inhibition of accumulation of hypoxia-inducible factor-1 α and VEGF expression [204] Blockage of NF- κ B pathway [216] Cell survival prolongation: reduces ROS formation, leads to PARP cleavage, and induces autophagy [217] Accumulation of ceramide and autophagy [232] Inhibition of APE/Ref-1, with decreasing of Ap-1/JunD, MMP-1, and iNOS, α -MSH [227, 230, 231] Reduction of AMP-activated protein kinase, COX-2, vasodilator-stimulated phosphoprotein, and VEGF [211, 233] Increasing the expression of thrombospondin-1 with decreasing of the VEGF-sensitive hypoxia inducible factor-1 α [42] Inhibition of lipopolysaccharide-induced epithelial-mesenchymal transition of IL-8 [235] Inhibition of NO production in VEGF-stimulated endothelial cells and of COX-2 induction [236]
Salicylic acid	Intracellular depletion of glutathione [237]
Tannic acid	Downregulation of UVB-induced IL-18 [261]

AMP adenosine monophosphate, AMPK-FOXO3 5' AMP-activated protein kinase/forkhead box protein O3, AP-1 activator protein-1, AP-1/JunD activator protein-1/JunD protein, Apaf-1 apoptotic protease-activating factor-1, APE/Ref-1 apurinic/apyrimidinic endonuclease/redox effector factor-1; ATP adenosine triphosphate, CD8+ T-cell cytotoxic T cell CD8 positive, COX-2 cyclooxygenase-2, COX-2 NF- κ B cyclooxygenase-2 expression through nuclear factor-kappa B, DNA deoxyribonucleic acid, dUTP 2'-deoxyuridine 5'-triphosphate, G1 Gap 1, ICAM-1 intercellular adhesion molecule-1, IFN- γ interferon gamma, IGF-1 insulin growth factor-1, IL-1 β interleukin-1 beta, IL-6 interleukin-6, IL-8 interleukin-8, IL-18 interleukin-18, iNOS inducible nitric oxide synthase, Ki-67 protein Ki-67, MAPK mitogen-activated protein kinase, MCP-1 monocyte chemoattractant protein-1, MMP-1 metalloproteinase-1, α -MSH alpha-melanocyte-stimulating hormone, NF- κ B nuclear factor-kappa B, NO nitric oxide, Nrf2 nuclear factor-like 2, p-4EBP1 phosphorylation of eukaryotic translation initiation factor 4E binding protein-1, p38 protein p38, PARP

poly ADP (adenosine diphosphate) ribose polymerase, *PCNA* proliferation cell nuclear antigen, *PGE-2* prostaglandin E2, *ROS* reactive oxygen species, *TLR-4* toll-like receptor-4, *TNF- α* tumor necrosis factor alpha, *TUNEL* terminal dUTP nick end labeling, *UVA* ultraviolet A, *UVB* ultraviolet B, *VEGF* vascular endothelial growth factor

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