Send Orders for Reprints to reprints@benthamscience.ae

Current Medicinal Chemistry, 2019, *Volume, Page Enation*

ARTICLE TYPE

Phenolic Compounds in Prevention and Treatment of Skin Cancers: a review

Francesca Gado[a], Maria Digiacomo[a,b*], Jasmine Esposito Salsano[a,c], Marco Macchia[a,b] and Clementina Manera[a,b]

[a]*Department of Pharmacy, University of Pisa, Pisa, Italy.* [c]*Interdepartmental Research Center "Nutraceuticals and Food for Health", University of Pisa, Pisa, Italy.* [b]*Doctoral School in Life Sciences, University of Siena, Siena, Italy*

ARTICLE HISTORY

Received:
Revised:
Accepted:

DOI:

Abstract: Several clinical studies have shown that exposure of skin to solar ultraviolet (UV) radiation causes adverse effects, such as inflammation, oxidative stress and DNA damage. As a result, different skin disorders can arise among which skin cancer, including non-melanoma skin cancer (NMSC) and melanoma (MM). Phenolic compounds are plant-derived secondary metabolites with a well-known antioxidant activity, able to counteract the negative effects of UV radiation. In this review we discuss the effects of some selected phenols on NMSC and MM, demonstrating that they can be useful in the prevention and in the treatment of these types of tumors. Moreover, we report the mechanisms by which these phenols carry out their antitumor action. *In vitro* and *in vivo* studies have highlighted that many phenols are capable of inducing photoprotection, apoptosis and autophagy. They can also reduce DNA methylation, tumorigenesis, tumor incidence and proliferation. Moreover, we describe some examples of plant extracts, whose anticancer activity appears to be better than that of single phenols. A great concordance of results emerged, despite the differences in experimental methods. Therefore, the knowledge compiled here could provide the basis for conducing some well-organized clinical trials to validate the chemopreventive and the therapeutic potential of some phenolic compounds in patients with NMSC and MM.

Keywords: skin cancer, phenolic compounds, oxidative stress, phytoextract, melanoma, chemoprevention, non-melanoma skin cancer.

1. INTRODUCTION

Skin cancer represents the most common human malignancy. The principal classes of skin cancer are cutaneous melanoma (MM) and non-melanoma skin cancer (NMSC). MM and NMSC differ primarily for the cells type in which they develop, as NMSC evolves in the keratinocytes of the epidermis, while MM in melanocytes. Skin cancer has a high survival rate and is generally treatable if diagnosed immediately; however, the metastatic form has an unfavorable prognosis. The incidence of both MM and NMSC has been increasing over the past decades. MM is less frequent but presents high mortality. It was demonstrated that both MM and NMSC are caused by ultraviolet (UV) radiations exposure, mainly UVA and UVB. UVA is the longest wavelength (320–400 nm) with the least energy, UVC the shortest (200–290 nm) but with the highest energy and UVB has a value between UVA and UVC (290-320 nm) with medium energy. UVC is completely absorbed by atmospheric ozone, while UVA and UVB are absorbed by the ozone layer for 5-10% and 90-95% respectively, and therefore reach the earth's surface. UVA rays can penetrate through the epidermis into the dermis during skin exposure while UVB rays are absorbed in the epidermis [1]. UVB radiation damages directly DNA through the formation of cyclobutane pyrimidine dimers (CPDs) and pyrimidine-pyrimidone 6-4 (6-4PP) photoproducts due first to cleavage of internal 5–6 double bonds and after to creation of abnormal covalent bonds between adjacent pyrimidines (figure 1) [2]. More specifically, thymine–cytosine and cytosine–cytosine dimers are reported to be the most oncogenic CPDs since their mutations were found, in UV irradiated cancer cells, in the tumor suppressor gene of the protein p53 [3]. Indeed, CPDs are involved in the suppression of immune system and in skin carcinogenesis. CPDs and 6-4PP are highly mutagenic but CPDs are less efficiently repaired than 6-4PP photoproducts [4]. Regarding

* Address correspondence to this author at the Department of Pharmacy, University of Pisa, via Bonanno 6, 56126 Pisa; Tel/Fax: +39 050 2219594/ +39 050 2210680 E-mails: maria.digiacomo@unipi.it.

0929-8673/19 $58.00+.00

6-4PP, these dimers are unstable, and thanks to the absorption of UV wave-lengths of around 320 nm, they shift into the more stable so-called Dewar valence isomers (figure 1).[5]

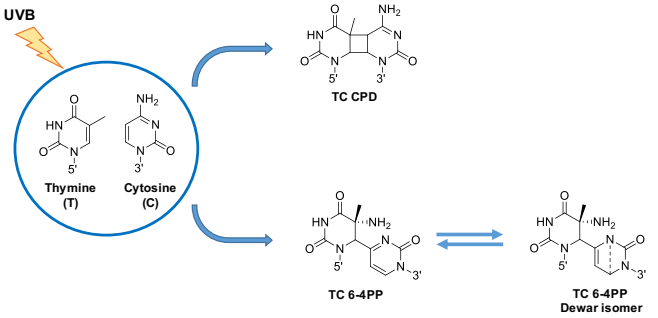


Fig. (1). Chemical structure of the main UVB-induced photoadducts cyclobutane pyrimidine dimers (TC CPD), pyrimidine-pyrimidone 6-4 (TC 6-4PP) and TC 6-4PP Dewar isomers produced from Thymine (T) and Cytosine (C).

The presence of abnormal covalent bonds between adjacent pyrimidines (CPD, 6-4PP, and Dewar isomers) inhibits polymerase transcription and arrests replication, which can lead to the activation of the p53 protein inducing apoptosis in healthy keratinocytes [6]. UV radiations induce also damages in RNA bases, especially during RNA transcription and translation with harmful consequences. More specifically, mutations in mRNA may be responsible of the production of dysfunctional proteins [7]. UVA radiation generates reactive oxygen species (ROS) that directly damage proteins, lipids, and DNA. The excessive formation of ROS induces oxidative stress that is involved in carcinogenesis as amply documented [8]. Therefore, targeting ROS-induced oxidative stress could represent a useful approach in cancer treatment.

In this review, we summarize the knowledge about the involvement of UV radiation and oxidative stress in onset and development of skin cancers. Furthermore, the literature regarding the antioxidant role of polyphenolic compounds in the prevention and treatment of skin cancers is reviewed by reporting the studies published in the last ten years.

1.1. Melanoma

MM was the fifth most common malignancy in men and the sixth most common in women in the United States in 2017 [9]. Among all deaths for skin cancer, in 2017 in the United States, approximately 72% is related to MM [9]. However the 5-year relative survival for MM is 92%, and in the case of primary MM without lymph node involvement, it even reaches 98% [10]. The exposure to UV light provokes variations in particular genes (polymorphisms) responsible of the defensive response of the skin to UV light. In particular, UV radiation induces genetic changes in the skin, damages cutaneous immune function, increments the production of growth factors, and causes the formation of ROS. MM, for example, is characterized by a many ultraviolet-signature mutations, such as C → T (caused by UVB) or G→T (caused by UVA) transitions [11]. These polymorphisms increase the risk of MM considerably. Consequently, due to exposure to UV light, skin pigmentation improves through the action of α-melanocyte–stimulating hormone (α-MSH) on its receptor, the melanocortin receptor 1 (MC1R), which stimulates intracellular signaling in melanocytes and increases the production of melanin. Germ-line polymorphisms in the MC1R gene are often present in light-skinned and redheaded people, and they lead to a reduction of the activity of the receptor, and to an increase of the predisposition to MM [12]. The appearance of MM is generally linked to frequently intermittent exposure to the sun. Similarly, to other cancers, the development of MM is due to the activation of oncogenic signal transduction. Malignant transformation into MM can occur following mutations such as the activating BRAFv600 (Val600), which has been already found in benign formations, or additional mutations, such as mutations in the telomerase reverse-transcriptase (TERT) promoter, tertiary mutations in cell-cycle controlling genes (cyclin-dependent kinase-inhibitor 2A [CDKN2A]) or chromatin-remodelling (AT-rich interaction do main [ARID]1A, ARID1B, ARID2). Metastatic MM progression is associated with mutations in phosphatase, tensin homologue (PTEN) or tumor-protein p53 (TP53) [13]. However, in MM the overstimulation of the cellular pathways, the main of which are the activated mitogenic-protein-kinase (MAPK) pathway, phosphoinositide-3-kinase (PI3K), proteinkinase-B (AKT), PTEN and the mammalian target pathway of rapamycin (mTOR), can occur. Frequently the MM cells avoid the immune system.

1.2. Non-Melanoma Skin Cancer

Although various types of skin cancer, such as cutaneous lymphoma, adnexal tumors, Merkel cell carcinomas and other rare skin cutaneous neoplasms are included among the NMSCs, this term conventionally refers to basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). BCC affects the basal layer of epidermis and manifests mainly in the face and back of the hands, while SCC develops in squamous (or spinosum) layer of epidermis and appears on the head and neck. BCC has slow growth and local diffusion with little or no metastasis, whereas SCC can develop into invasive SCC with metastasis [14]. The early phase of SCC is called actinic keratosis. In general, the transition from the pre-cancer actinic keratosis to SCC occurs in several steps. In the first stage of actinic keratosis, UV radiation causes DNA damages and mutations. Then aggregates of small transformed cells are formed, which over time generate aggregate forms of keratinocytes, characterized by atypia and pleomorphism. The lesions, at this point, can reach the dermis by developing SCC, and can also metastasize [15]. Despite a more careful skin protection during sun exposure, in the last years, the incidence of this type of tumor continues to grow. For example, the incidence of BCC alone increases by 10% each year, and soon the spread of this cancer will be comparable to that of all other type of cancers combined together [16]. UV radiation exposure is the main risk factor for the pathogenesis of SCC and BCC, with a more pronounced effect on SCC. While SCC is associated with cumulative sun exposure throughout life, BCC is linked to intermittent exposure to the sun [17]. In addition, the involvement of formation of ROS in carcinogenesis is always documented and evident [8].

Although the skin carcinogenesis process is not fully explained, many keratinocyte specific proteins that could be implicated in carcinogenesis have been described. Among these, IL-1 beta may play an important role, modulating the production of keratinocyte in inflammation and reducing the keratinocyte differentiation and motility proteins. Moreover, IL-1 determines a higher expression of angiogenetic and anti-apoptotic proteins.

1.3. Oxidative stress

The imbalance between generation and elimination of ROS and reactive nitrogen species (RNS) is named oxidative stress. ROS and RNS can derivate from normal metabolism of skin cells or from the exposure to environmental agents, including UVA and UVB radiations. In physiological conditions, ROS, such as superoxide anion (O_2-) and H_2O_2 are formed at low concentrations from the normal metabolism of skin cells as byproducts of the electron-transportation chain functioning (figure 2). Keratinocytes and fibroblasts are the main producers of 'mitochondrial' ROS in the skin [18]. Intracellular superoxide (O_2-) is primarily produced from the oxidation of nicotine amide adenine dinucleotide reduced form (NADPH) by oxidase enzymes (NOX) or from electron leak due to the aerobic respiration in the mitochondria [19]. Superoxide anion O_2·- can dismutate spontaneously or by superoxide dismutase (SOD) into H_2O_2, which gives OH- through Fenton's reaction or H_2O thanks to a catalase. From OH·- other ROS, such as carbonyl radical (R·), peroxyl radical (ROO·) and alkoxyl radical (RO·), can be obtained [20]. Regarding RNS, they are endogenously produced by the conversion reaction of arginine into citrulline mediated by nitric oxide synthase (NOS), which in particular gives NO. In the blood, NO can quickly interact with O_2·- to yield another important ROS, peroxynitrite (ONOO-) (figure 2) [21].

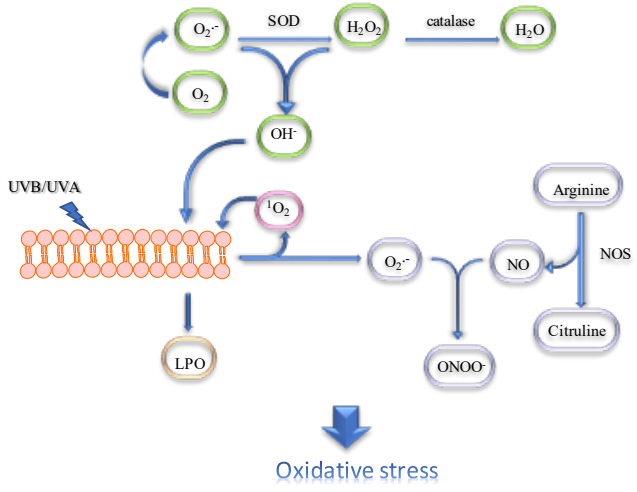


Fig. (2). ROS formation and antioxidant defense in skin cells.

1.4. Phenolic compounds

Phenolic compounds are secondary metabolites of plants, with well-known anti-oxidant activity and inhibitory effects on cancer cells. It was amply demonstrated that they induce apoptosis, inhibit proliferation, angiogenesis and metastasis, and modulate the immune system in cancer cells and tissues. Many studies have been conducted on single molecule or on their combination or on association with cancer drugs leading to some interesting results (Table 1).

It is known that the biological activity of phenolic compounds could be affected by metabolism. They are transformed by various enzymes in the liver, small intestine and colon; some are absorbed in the digestive system and subjected to conjugation, while those that are not absorbed are biotransformed by the colon microbiota in order to allow their absorption in the intestine. For topical treatments of the skin, it is necessary to consider the hydrophobic characteristics of the skin and then formulate a convenient hydrophobic, organic and cream based vehicle to facilitate the penetration of phenolic compounds. Recently new bioengineering methods or nano and macro derivations have been designed to improve bioavailability, biological activity and efficacy of phenolic compounds.

1.4.1 Epigallocatchin-3-gallate

Epigallocatchin-3-gallate constitutes the most abundant polyphenol present in the green tea (50%-80%) [37]. Topical application of green tea or white tea extracts is able to protect human skin from UVB and UVA damage [38]. In particular, epigallocatchin-3-gallate showed a protective profile against UVB-induced infiltrating leukocytes, antigen-presenting cells, and oxidative stress in mice [39]. Furthermore, topical application of epigallocatchin-3-gallate prevented photocarcinogenesis in wild-type mice, but not in interleukin (IL)-12 knockout (KO) mouse model UVB exposed. These data suggested that the photoprotective profile of epigallocatchin-3-gallate was via IL-12-dependent, a cytokine involved in DNA repair through the nucleotide excision repair (NER) enzymes [40].

In A431 and SCC13 skin cancer cells, epigallocatchin-3-gallate showed to inhibit β-catenin signaling, determining the decrease of tumor cell viability, inflammatory mediators, and an increase in cell death [41]. Moreover, epigallocatchin-3-gallate reduced DNA methylation levels in A431 cells, acting as epigenetic modulator agent [42]. This polyphenol decreased cell invasion through demethylation of RECK, a tumor suppressor gene that negatively regulates matrix metalloproteinases, in two human oral SCC cell lines (HSC3 and SCC9) [43]. Moreover, epigallocatchin-3-gallate decreased UVB-induced phosphorylation of MAPK and collagen degradation downregulating MMP-1, -8, and -13 in human dermal fibroblasts [44]. The inhibition of UVB-mediated phosphorylation of MAPK induced after treatment with epigallocatchin-3-gallate, was also confirmed in skin equivalents (consisting of epidermal keratinocytes and dermal fibroblasts) [45]. In these models, the authors also showed that the pre-treatment with epigallocatchin-3-gallate resulted in decreased UVB-induced p53 and Fas expression [45]. Topical application of epigallocatchin-3-gallate seems to be able to induce apoptosis in tumors inhibiting tumor proliferation in UVB exposed SKH-1 hairless mice [46]. The first two clinical studies on epigallocatchin-3-gallate were published in 1999 and in 2001. The skin of healthy adult volunteers was treated with topical application of epigallocatchin-3-gallate 30 minutes before UVB exposure. The authors showed that topical treatment with

epigallocatchin-3-gallate reduced UVB-induced erythema, infiltration of leukocytes, myeloperoxidase activity, PGE2, NO and H_2O_2 and increased antioxidant enzyme glutathione peroxidase levels compared to untreated skin, suggesting an anti-inflammatory effect [47]. Furthermore, a randomized double-blind, placebo-controlled phase II clinical trial of topical epigallocatchin-3-gallate was conducted in 2003. A total of 51 subjects completed the 12-week study, in which the agent was applied to one forearm with actinic keratosis and placebo ointment to the other forearm nightly. There were no statistically significant differences between the treated and control groups. In this study, epigallocatchin-3-gallate showed no clinical activity for the treatment of actinic keratosis [48]. About UVA radiation, Sevin *et al*. described that topical application of epigallocatchin-3-gallate on rats could prevent acute UVA damage on skin by reducing sunburn cells formation and dermo-epidermal activity [49]. Zhang *et al*. demonstrated that epigallocatchin-3-gallate is able to inhibit the tumor necrosis factor receptor-associated factor (TRAF6), which is involved in signaling transduction pathways, as NF-κB and MAPK pathway [50]. In particular, TRAF6 activates NF-κB pathway in response to pro-inflammatory cytokines through its E3 ubiquitin ligase activity, which exerts important functions in tumorigenesis. The authors have highlighted that TRAF6 was over-expressed in clinical MM tissues and MM cell lines, such as SK-MEL->5 and -28. Furthermore, TRAF6 knockdown, dramatically reduced tumor cell growth and metastasis [50]. Moreover, *in vitro* and *in vivo* studies have shown that epigallocatchin-3-gallate suppressed the E3 ubiquitin ligase activity of TRAF6, preventing the regulation of NF-κB pathway activation by TRAF6. Furthermore, epigallocatchin-3-gallate inhibited the migration and invasion and also the cell growth of MM cells [50]. As demonstrated in other studies, in MM cells (A374 and Hs-294T) epigallocatchin-3-gallate was able to arrest the cell cycle inducing apoptosis. Nihal *et al*. have highlighted that this effect is possible thanks to the capability of epigallocatchin-3-gallate to modulate cki-cyclin-cdk network and Bcl2 family proteins [51].

1.4.2. Curcumin

Curcumin is a polyphenolic pigment obtained from the rhizome of *Curcuma longa* L. It is employed in traditional Chinese medicine, as antimicrobial, antioxidant, anti-tumor, anti-inflammatory agent and for the treatment of psoriasis [52].

It is known that curcumin is able to inhibit tumor cells through the modulation of different signaling pathways involved in cell survival, proliferation and apoptosis but some of these mechanisms are not completely clear [53]. In SCC, curcumin showed the ability to decrease cell growth and to induce apoptosis in an *in vitro* model of SCC (A431) through the inhibition of p-STAT-3 (signal transducer and activator of transcription 3) [54]. The activity of curcumin against SCC was validated in a mouse model of xenograft tumors for human SCC SRB12-p9, where curcumin decreased tumor size after both topical and systemic administration [55]. Furthermore, curcumin showed an interesting photoprotective action against UVB-induced skin tumor formation in SKH-1 hairless mice skin. Indeed, topical application of curcumin prior to UVB irradiation caused delay in tumor appearance, multiplicity, and size probably partially due to the significantly inhibition of NF-κB, COX-2, PGE2, and NO levels [56].

Several *in vitro* and *in vivo* studies, have documented the anti-MM activity of curcumin, and in addition phase I and phase II clinical trials confirmed the safety and the therapeutic efficacy of curcumin in patients with MM [57]. Curcumin induces apoptosis but the exact mechanism is not clear. As reported by Odot *et al*., curcumin seems to induce apoptosis in MM cells through the activation of the mammalian STE20-like kinase 1 (MST1), a serine/threonine kinase activated during apoptosis [57]. Curcumin, consequently to ROS formation, activates MST1, which after determines JNK activation, Foxo 3a nuclear accumulation and Bim-1 expression, so as to give apoptosis [58]. Other studies demonstrated that curcumin is able to inhibit NF-κB, a pro-survival pathway, and activate Fas-initiated Fas-Associated protein with Death Domain (FADD), a death receptor pathway [59]. Recently Qui *et al*. have shown the capability of this polyphenol to open a mitochondrial permeability transition pore (mPTP) inducing cytotoxicity in MM cells [60].

1.4.3. Resveratrol

Resveratrol is a non-flavonoid polyphenol compound contained in grapes, nuts, and berries.

Resveratrol plays a photo-chemopreventive role in the UV-induced skin cancer with different molecular mechanisms, one of which is the ability to induce autophagy [61]. Autophagy is a process whereby the cell removes damaged and potentially carcinogenic components. A marker of autophagy is represented by light chains 3 (LC3) protein, which makes up the autophagosomal membrane. During autophagy, the autophagosome are fused with the lysosome to form the autolysosome, then the contents of the autolysosome, and their internal membrane are degraded. As reported by Vitale and collaborators, resveratrol is able to increase the conversion of the LC3 protein from the LC3I form to the LC3II form, a key event in the formation of autophagosome [61]. Therefore resveratrol exerts its photochemopreventive effects by increasing autophagy. The authors showed that pretreatment with resveratrol on UVB-irradiated human skin keratinocytes cell line (HaCaT) also reduces the production of ROS and enhances UVB-induced apoptosis modulating caspase-8 and poly-(ADP- Ribose) polymerase (PARP) cleavage [61]. Bach and collaborators showed that resveratrol induced premature senescence that is associated with a blockade of autolysosome formation, in a *in vitro* model of SCC (A431 cell line), downregulating Rictor, a component of mTORC2 [62]. Moreover, it was shown, in *in vivo* studies on p53+/−/SKH-1 mice, that Rictor is overexpressed in UV-induced SCC and that the administration of resveratrol provokes its reduction. Therefore it was possible to demonstrate that resveratrol attenuates autophagic process via Rictor [62]. In an another study, it was shown that resveratrol in A431 cells, determined an upregulation of p53 and ERK, and a downregulation of survivin, a member of IAP (inhibitor of apoptosis) protein, increasing apoptosis [63]. Resveratrol has been also investigated in MM cells line, in which it inhibits

proliferation. A study has demonstrated its ability to inhibit the growth of two human MM cell lines, SK-mel28 and A375 cells, inducing apoptosis through mechanisms which involve different kind of MAP kinases [64].

Moreover Gatouillant *et al*. have demonstrated the ability of resveratrol to determinate apoptosis and inhibit the growth of a doxorubicin-resistant B16 MM cell subline (B16/DOX) [65]. A recent study has described an important capability of resveratrol to inhibit the invasive and the migratory properties of MM through the down-regulation and inactivation of Akt/PKB, a serine-threonine kinase, which plays a key role in the development of malignancy and in its metastatic behaviour [66].

1.4.4 Carnosol

Carnosol is a natural phenolic diterpene contained in rosemary and sage, known for its anti-inflammatory, anti-oxidant and anti-cancer properties.

In a recent scientific paper, the authors demonstrated that carnosol reduced UVB-induced ROS level in a dose-dependent manner in irradiated HaCaT cells. Moreover, carnosol significantly decreased NF-kB activation and the phosphorylation levels of both H2A histone family member X (H2AX) and checkpoint kinase 1 (Chk1) which are two important markers of DNA breakage and damage. In addition carnosol inhibited the CPD formation in irradiated cells and keratinocyte transformation upon UVB radiation [67]. As clarified by the same authors, UVB radiations induce activation of NF-κB, a pro-oncogenic factor whose expression resulted elevated in skin cancer cells, through the activation of nitric oxide synthases (NOS) [68]. In particular, nitric oxide (NO•), formed from NOS, reacts with O_2•− to give peroxynitrite (ONOO−), with consequently pERK activation, eukaryotic initiation factor 2 (eIF2α) phosphorylation, down regulation of IκB synthesis and then NF-κB activation. Carnosol inhibited NADPH oxidase (NOX) reducing O_2•− and ONOO− and consequently down-regulating NF-κB in HaCaT irradiated cells [68]. In a recent work the effects of carnosol in MM have been highlighted. The results of this study showed that carnosol strongly provoked apoptosis against human MM G361 cells in a dose- and time dependent manner causing an increasing of ROS level and ROS-dependent inhibition of STAT3 signaling pathway [69]. Moreover, in metastatic mouse MM B16F10 cells *in vitro,* carnosol inhibited the invasion, targeting matrix metalloproteinase-mediated cellular events [70]. Carnosol, also, inducts G2/M phase cell-cycle arrest, through the alteration of cyclin A and B1 levels [71].

1.3.5. Syringic acid

Syringic acid is a phenolic acid often found in fruits and vegetables but also in wine and in extra-virgin olive oil.

Ha and collaborators showed that syringic acid is able to significantly suppress phosphorylation of MAPKs, AKT and EGFR signaling, in UVB-irradiated HaCaT cells [72]. They also demonstrated the activity of syringic acid as inhibitor of NADPH oxidase (NoX), an enzyme importantly implicated in the formation of ROS. In particular, syringic acid suppressed EGFR phosphorylation but it did not alter their

expression levels and the authors showed that syringic acid significantly increased protein tyrosine phosphatase-kappa (PTP-κ) activity [72]. Indeed, it is known that PTP-κ regulates the Erk effector downstream of EGFR, which is a critical mediator of keratinocyte proliferation and survival, through regulation of EGFR phosphorylation/activation [73]. The EGFR activation mediated by UVB was found to be closely related to the phosphorylation of EGFR induced by ROS production [74]. Therefore, the increase in PTP-κ levels leads to a reduced Erk activation, to an inactivation of EGFR and, consequently, to a decrease in the growth of keratinocytes. Furthermore, topical application of syringic acid reduced the tumor number by 17.7% at 0.2 mM and by 35.7% at 1 mM compared to the UVB-only irradiated group, and in addition down-regulated COX-2 and MMP-13 expression in the skin of SKH-1 hairless mice [72]. For these reasons, syringic acid exerts potent chemopreventive activity targeting the NoX/ROS/PTP-κ/EGFR axis in the UV-induced skin carcinogenesis [72].

1.4.6. Caffeic acid

Caffeic acid is a hydroxycinnamic acid, present in coffee and in different vegetables, fruits and herbs such as wine, turmeric, oregano, sage, cabbage, strawberry, apples, cauliflower, radishes and mushrooms.

Balupillai and collaborators demonstrated that caffeic acid prevents the formation of CPDs and improves the expression of PTEN both in human dermal fibroblasts (HDFa) and in mouse skin UVB-exposed, showing a photoprotective profile [75]. Furthermore, the same authors demonstrated that the activation of PTEN, induced by caffeic acid, prevented UVB-induced activation of PI3K/AKT [75]. It is known that elimination of CPDs occurs in NER pathway and that PTEN is a critical factor in the regulation of NER mechanism [76]. In particular, skin carcinogenesis could be stimulated by PTEN mutation or deletion, as PTEN is a tumor suppressor gene for skin cancer [77]. The photoprotective effects of caffeic acid were also correlated with the activation of peroxisome proliferating activated receptor-γ (PPAR γ) [78], and with the inhibition of STAT3 translocation [79], a transcription factor, which mediates the expression of genes associated with cell growth and apoptosis, in UVB exposed mouse skin. Indeed, both topical and intraperitoneal treatment with caffeic acid on one hand decreased LPO and inflammatory markers (iNOS, VEGF, transforming growth factor (TGF-β)) expression, while on the other hand both treatments enhanced antioxidant status and reduced tumor multiplicity in UVB exposed mice skin [78]. Finally, caffeic acid showed the ability to attenuate migratory capability and cancer stem cells-like phenotype in an *in vitro* model of malignant human keratinocyte (HaCaT), inducing phosphorylation of p38 and down-regulating NF-κB pathway [80]. Caffeic acid decreased also UVA-induced MMP-1 through the increase in antioxidant defense system in HaCaT cells [81]. The research of the effect of caffeic acid on SK-Mel-28 cells, revealed its capacity to decrease the cell viability, induce cell death by apoptosis, inhibit colony formation, modulate cell cycle and alter gene

expression of caspases. Therefore, caffeic acid showed an antitumor effect in human MM cells [82].

1.4.7. Ferulic acid

Ferulic acid is a hydroxycinnamic acid ubiquitously present in plants. It is not generally present in the free form, but as ester cross-linked with polysaccharides such as pectin in spinach and sugar beet and xyloglucans in bamboo, or with protein. Compared to other phenolic compounds, it is more easily absorbed into the body and it stays in the blood longer. Ferulic acid is considered to be a superior antioxidant [83], presenting low toxicity and many physiological functions, including anti-inflammatory and anticancer (in particular lung, breast, colon and skin cancer) activities [83]. Ferulic acid presents three different properties, it is a radical scavenger, an inhibitor of the enzymes which catalyzes free radical generation, and it is also able to enhance the scavenger activity of other enzymes [84]. UVA-mediated ROS formation is positively associated with increased MMP-1 activity and mRNA expression in HaCaT cells. In the cells pretreated with ferulic acid, UVA-mediated ROS formation and up-regulation of MMP-1 activity and mRNA are abolished. These effects could be due to transcriptional and post-translational regulation of antioxidant defenses such as glutathione (GSH), catalase and glutathione peroxidase (GPx) [81]. In MM cells, ferulic acid inhibited proliferation and blocked the PI3K-Akt pathway. Moreover, in a MM xenograft model *in vivo*, ferulic acid reduced growth associated with inhibition of angiogenesis. It was established that ferulic acid targets the FGFR1-mediated PI3K-Akt signaling pathway, leading to the suppression of MM growth and angiogenesis [85].

1.4.8. Ellagic acid

Ellagic acid is a polyphenolic compound belonging to the family of ellagitannins. It is present in high amounts in a variety of berries, pomegranates, grapes and walnuts. In the last decades, researchers' interest in tannins, including ellagitannins, has increased considerably. Their beneficial effects on human health and their activity towards many diseases have been highlighted. In particular, the antitumor potential of the fruits containing ellagic acid has been demonstrated in a variety of tumor models [86,87]. Hseu and collaborators showed that in HaCaT cells, ellagic acid increased cell viability suppressing UVA-induced ROS generation and MDA formation. Moreover, ellagic acid has been reported to present a protective effect against oxidative stress and apoptosis because it induces the expression of endogenous antioxidants, such as HO-1 and SOD, and of Nrf2. Ellagic acid simultaneously down-regulates Keap1 activity, resulting in Nrf2 translocation into the nucleus and in the activation of antioxidant genes [87]. Furthermore, always in UVB induced keratinocytes model (HaCaT), ellagic acid decreased proinflammatory mediators such as interleukin IL-1ß, IL-6, IL-8 and increased IL-10 that is an anti-inflammatory mediator [88]. In an *in vitro* study performed on three different metastatic MM cell lines (1205Lu, WM852c and A375) ellagic acid exerted inhibitory effects on cell proliferation, promoting G1 cell cycle arrest, inducing apoptosis and decreasing NF-κβ. These evidences suggest the potentiality of ellagic acid as a preventive and therapeutic agent against MM [89].

1.4.9. Rosmarinic acid

Rosmarinic acid is a water-soluble, naturally occurring hydroxylated compound, found in a variety of medicinally used herbs such as *Artemisia annua* L., *Calendula officinalis* L. and widely distributed in *Labiatae* herbs, which include rosemary, sweet basil, and perilla [90,91]. Similarly to ellagic acid, rosmarinic acid has been shown to possess mainly antioxidant and anti-inflammatory activities, but also antiviral and antibacterial properties [92]. In 2016, a study by Fernando and collaborators demonstrated the scavenger effect of rosmarinic acid on ROS. In general, polyphenol may be effective in photo-protection due to similarities between their structure and that of organic UV filters. Indeed, thanks to its ability to be absorbed within the UVB range, it can exert its cytoprotective activity increasing the viability of HaCaT cells. Moreover, rosmarinic acid has also been showen to increase Nrf2 levels, decreased by UVB exposure [93]. In 2014, Lembo and collaborators studied both ellagic acid and rosmarinic acid in HaCaT cells. Indeed, using UVB irradiation and different ellagic acid and rosmarinic acid incubation times, they demonstrated that both polyphenolis were able to modulate the expression of inflammatory mediators (tumor necrosis factor (TNF)-α, IL-6, IL-8, MCP-1, and IL-10) [88]. TNF-α plays an important role in the initiation and in the promotion of the inflammatory pathway following UVB irradiation, such as cell adhesion molecules, promotion of apoptosis, and activation of lymphocytes [94]. In this study, only rosmarinic acid, after 24h incubation immediately after UVB irradiation, was able to significantly reduce TNF-α expression. Conversely to TNF-α, other inflammatory mediators (IL-6, IL-8, monocyte chemoattractant protein-1 (MCP- 1)) were found to be reduced following the incubation with both rosmarinic and ellagic acids. Regarding IL-10, its role is the immunosurveillance of the initiation and progression of skin cancer. Rosmarinic acid and ellagic acid potentiated IL-10 expression after a 24h incubation period, presenting the highest increased if added immediately after irradiation [88].

1.4.10. Luteolin

Luteolin is a flavonoid with potential anti-oxidant activity. Luteolin induced protection against carcinogenic effects due to UVB irradiations. In normal human keratinocytes exposed to physiological doses of UVB irradiations, luteolin was able to control i) apoptotic signaling modifying the balance of Bcl2 (B-cell leukemia/lymphoma 2) -family members [95]; ii) proliferative activity decreasing phosphorylation of MAPKs and the Akt signaling pathway [96]; iii) the release of inflammatory actors, IL-1α, PGE2 [95], COX-2, activator protein-1, Nf-κB and tumor necrosis factor-α [96]. In addition, Byun and collaborators revealed that luteolin binds directly to protein kinase Cε (PKCε) and Src in an ATP-competitive manner [96]. An *in vitro* study conducted in A431 cells showed the ability of luteolin to control the epithelial mesenchymal transition (EMT) [97]. Finally,

luteolin suppressed tumor incidence, multiplicity, and overall size in SKH-1 hairless mice exposed to UVB [96]. Some authors demonstrated the inhibitory activity of luteolin on the proliferation, migration and invasion of A375 cells. In this study, both *in vivo* and *in vitro*, it has been highlighted that luteolin causes the apoptosis of A375 cells in a concentration-dependent manner, and also reduces the expressions of MMP-2 and MMP-9 and increases the expression of TIMP-1 and TIMP-2. Therefore luteolin can be a promising anti-cancer agent for the treatment of human MM [98].

1.4.11. Apigenin

Among flavonoids, also apigenin, in a mouse model, showed the ability to block skin tumorigenesis induced by the chemical carcinogens, 7,12-dimethylbenz[a]anthracene (DMBA) and 12-O-tetradecanoylphorbol-13-acetate (TPA) [99]. The mechanism of action of apigenin includes the inhibition of COX-2 [99] and the restoring of the silenced status of Nrf2, a crucial transcription factor that controls anti-oxidative stress defense system and is implicated in skin homeostasis [100]. Moreover, apigenin is able to inactivate STAT3, a transcriptional factor normally activated in human MM, which leads this disease to a metastatic behavior. In this way, apigenin inhibits migration and invasion of cells in murine MM exerting thus an anti-metastatic activity. For this reason, apigenin is considered a promising target for the treatment of MM [101].

1.4.12. Licochalcone B

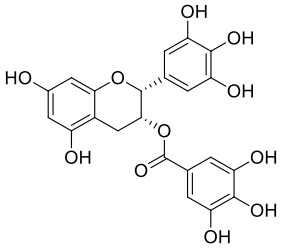
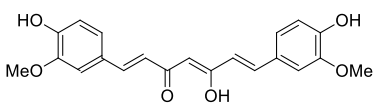
Licochalcone B (Lico B) is a chalconoid compound present in the root of *Glycyrrhiza inflate*.

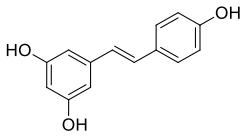
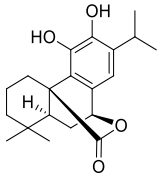
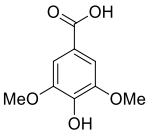
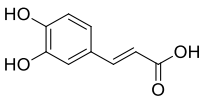
It was reported that Lico B is able to inhibit cell proliferation and to induce cell cycle arrest and apoptosis in tumor cells [102]. In particular, in a recent work the apoptotic effect of Lico B in SCC cells was studied. The authors have evaluated the action of Lico B on extrinsic and intrinsic apoptotic pathways [102]. In relation to intrinsic pathways, they considered the apoptotic effect of Lico B through Sp1 regulation. Sp1 is a zinc finger transcription factor that provides to cell cycle progression, but also regulates transcription of genes involved in proliferation, angiogenesis, cell cycle progression and inflammation. Lico B downregulates Sp1 in time dependent and concentration-dependent manners [102]. Moreover, the authors have investigated the mechanism involved in Sp1-mediated apoptosis, then, they studied the effects of Lico B on the expression of proteins p21, p27, Mcl-1, and Survivin correlated to cell cycle-arrest and survival [102]. Lico B increased the expression of the proteins regulators of cell cycle progression, p21 and p27. Both these proteins act as cell cycle inhibitors. Moreover, Lico B reduces the levels of anti-apoptotic proteins such as Mcl-1 and Survivin. These proteins are usually overexpressed in cancer, resulting in suppression of apoptosis, and in a consequent development of cancer itself. In addition, the authors have demonstrated that Lico B promotes apoptosis through the extrinsic pathway, stimulating the expression of apoptosis genes, CHOP, DR4, and DR5 [102]. As derived from these studies, Lico B is able to promote apoptosis through both intrinsic and extrinsic pathway and therefore, it could play an important role in the treatment of NMSC. Kang *et al*. have investigated the effect of Lico B on MM cells line (A375) and SCC cells line (A431). Lico B have shown the ability to inhibit cell proliferation and to induce apoptotic cell death in both A375 and A431 cells. The mechanisms of action of Lico B include increase of sub-G1 cells (apoptotic cells), reduction of Sp1 protein, induction of mitochondrial membrane depolarization, endoplasmic reticulum stress, and expression of death receptor (DR). Moreover, Lico B enhances multicaspase activation, increases pro-apoptotic proteins (Apaf-1 and Bax) and decreases anti-apoptotic proteins (Bid and Bcl-2). In summary, all these effects lead to apoptosis by both the intrinsic and extrinsic apoptotic pathways in A375 and A431 cells. These findings suggest that Lico B may be an interesting compound potentially useful not only in NMSC but also in MM skin cancer [103].

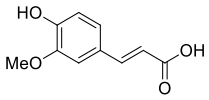
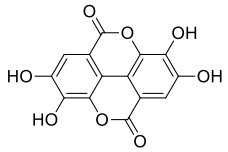
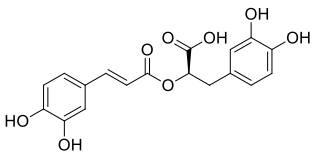
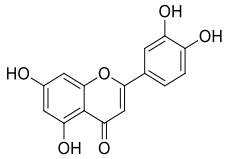
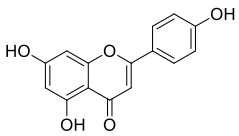
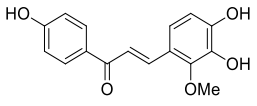
1.4.13. Proanthocyanidins

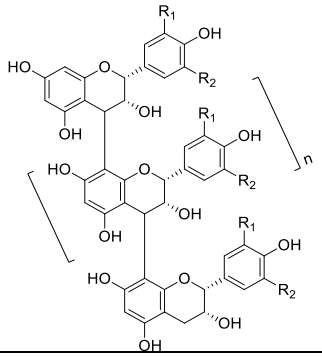
Proanthocyanidins are natural molecules found in vegetables, fruits, seeds, flowers, bark and nuts. They are dimers, trimers, tetramers and oligomers of monomeric epicatechins or catechins. The principal type of proanthocyanidins are the procyanidins, formed by epicatechin monomers, while the less common are prodelphinidins that are constituted by epigallocatechin subunits. Tests conducted on SKH-1 hairless mice have shown that the administration of a diet rich in proanthocyanidins (0.2 and 0.5% weight / weight) for 24 weeks has a preventive effect on the development of UVB-induced skin cancer. In particular, proanthocyanidins seem to reduce the incidence and multiplicity of the tumor and to slow down its growth. Moreover, the authors have shown that a diet with proanthocyanidins (0.5%, p / p) can repair the CPD, that constitutes one of the main damages induced on the DNA by UVB radiations [104]. It seems that administration of proanthocyanidins with diet increases the expression of NER genes contributing to repair CPD in mouse skin [104]. Many studies on the *Vitis vitifera* L. have highlighted the presence of proanthocyanides endowed with antitumor activity in animal models and cell cultures. In particular, as reported in a recent work, seed and peel extracts of *Vitis vinifera* L. showed cytotoxic activity in A431 cells while they are no toxic in the non-tumor HaCaT cell line [105]. At low concentrations of extracts, there is a morphological change of the A431 cells, thus showing a dose dependent toxicity. The same authors have documented that *Vitis vinifera* L. seeds and peel extracts have provoked early and late apoptosis in A431 cells. Several *in vitro* studies demonstrated that proanthocyanidins decrease the viability and induce apoptotic cell death in human MM cell lines, A375 and Hs294t, without toxicity to normal human epidermal melanocytes [106]. The apoptotic activity is due to activation of caspase-3, caspase-9 and PARP. The inhibition of MM cell growth by grape seed proanthocyanidins is imputable to the reduction in the levels of β-catenin, as it is confirmed by *in vivo* studies carried out using *in vivo* tumor xenograft model.

Table 1 Main phenolic compounds and their effects in NMSC and MM

Phenolic compounds	Structure	Biological process	Models	References
Epigallocatchin-3-gallate		⇑ Photoprotection	Mice + UVB	39
		⇓ Cell viability ⇓ Inflammatio	A431 cells SCC13 cells	40
		⇓ DNA methylation ⇓ Cell invasion	A431 HSC3 cells SCC9 cells	41, 42,43
		⇑ Photoprotection	Fibroblast+ UVB	44
		⇑ Photoprotection	Dermal skin equivalents (keratinocytes and fibroblasts) +UVB	45
		⇑ Apoptosis ⇓Tumour proliferation	SKH-1 hairless mice + UVBA374 Hs-294T	46
		⇑ Immune stimulation ⇑ Photoprotection ⇑ Antioxidant defense	Human subjects + UVB	47,48
		No clinical activity	Human subjects with actinic keratoses	47,48
		⇑ Photoprotection	Rats + UVA	49
		⇓ Cell growth ⇓ Metastasis ⇓ Cell migration ⇓ Cell invasion	SK-MEL->5 and -28	50
		⇑ Apoptosis	A-375, Hs-294T and G-361	51
Curcumin		⇓ Cell grow ⇑ Apoptosis	A431	54
		⇑ Cytotoxicity	Mouse model of xenograft tumours for human squamous cell carcinoma SRB12-p9	55
		⇓ Tumour size ⇑ Photoprotection ⇓ Inflammation	SKH-1 hairless mice + UVB	56

		⇑ Apoptosis	B16-R	57
		⇑ Apoptosis	WM-115 B16 MMRU PMWK	58 59
		⇑ Apoptosis	WM-115	60
Resveratrol		⇑ Apoptosis ⇑ Autophagy	HaCat + UVB	61
		⇓ Autophagy ⇑ Senescence	A431 Mice + UVB	62
		⇑ Apoptosis	A431	63
		⇓ Cell growth ⇑ Apoptosis	SK-mel28 A375	64
		⇑ Apoptosis ⇓ Cell growth	B16/DOX	65
		⇓ Cell invasion ⇓ Cell migration	B16F10	66
Carnosol		⇑ Photoprotection	HaCat + UVB	67
		⇓ Cell invasion ⇑ Apoptosis	G361	68
		⇑ capacity for ionizing radiation-induced damage	B16F10	70
		⇓ Cell invasion ⇓ Cell viability	B16F10	71
Syringic acid		⇑ Photoprotection ⇓ Inflammation	HaCat + UVB	72, 73
		⇑ Photoprotection ⇓ Tumor number	SKH-1 hairless mice + UVB	72, 73
Caffeic acid		⇑ Photoprotection	HDFa + UVB	75
		⇑ Photoprotection	Mice skin + UVB	75
		⇓ Inflammation ⇓ Tumour number	Mice skin + UVB	78
		⇑ Photoprotection	Malignant HaCat	80
		⇓ Cancer stem-cells-like phenotype ⇓ Migration	HaCat + UVA	81
		⇑ Antioxidant defense	HaCat + UVA	81

		⇑ Apoptosis ⇓ Cell viability	SK-Mel-28	82
Ferulic acid		⇑ Antioxidant defense ⇓ Cell growth ⇓ Cell angiogenesis	HaCat + UVA mice with B16F10 xenografts	81 85
Ellagic acid		⇑ Antioxidant defense ⇓ Inflammation ⇑ Apoptosis ⇓ Cell proliferation	HaCat + UVA HaCat + UVB 1205Lu WM852c A375	87 88 89
Rosmarinic acid		⇓ Inflammation ⇑ Antioxidant defense ⇑ Cell viability	HaCat + UVB HaCat + UVB	88 93
Luteolin		⇑ Apoptosis ⇓ Inflammation ⇓ Tumour size ⇓ Tumour incidence ⇓ EMT ⇑ Apoptosis ⇓ Cell migration ⇓ Cell proliferation ⇓ Cell invasion	Primary human keratinocytes + UVB SKH-1 hairless mice + UVB A431 A375	95, 96 96 97 98
Apigenin		⇓ DNA methylation ⇓ Inflammation ⇓ Tumorigenesis ⇓ Cell invasion ⇓ Cell migration	DMBA/TPA-treated SKH-1 mice Mice + B16F10	99 101
Licochalcone B		⇑ Apoptosis ⇓ Cell viability ⇑ Apoptosis ⇓ Cell proliferation	A431 A375, A431	102 103

Proanthocyanidins		⇓ Tumour incidence	SKH-1 hairless mice + UVB	104
		⇓ Cell viability ⇑ Apoptosis	A431	105
		⇑ Apoptosis ⇓ Cell viability ⇓ Cell growth	A375, Hs294t	106

1.5. Phytoextracts

Plant extracts are often more effective than isolated compounds. The extracts are constituted by a complex mixture of phytochemicals, which favorable interact within each other, and moreover could target multiple molecular pathways improving the biological response (Table 2).

In the next paragraphs, we report some examples of extracts with an interesting anti-tumor activity against MM and NMSC.

1.5.1. Rosmarinus Officinalis

Rosmarinus officinalis, commonly known as rosemary, is an evergreen herbal, typical of Mediterranean Countries. Different studies have demonstrated that rosemary extracts have chemoprotective [107], anti-neoplastic [108,109] and anti-proliferative activity in a number of different tumour cells lines [110-112] and also important anti-oxidant [108] and anti-inflammatory properties due to the presence of polyphenols [113]. The main polyphenols contained in rosemary extract (alcoholic or hydroalcoholic) are rosmarinic acid, carnosol and carnosic acid, but there are also other polyphenolic compounds such as apigenin, luteolin, caffeic acid and scutellarin [107].

Most of these polyphenols are already assayed individually, demonstrating an efficacy in different cell lines [114], including MM [115] and NMSC [116]. However important studies have shown that the extract is more effective than the single polyphenols, especially *in vitro* MM models [107]. Cattaneo *et al*. have documented that a 65% hydroalcoholic extract of *Rosmarinus officinalis* L. has a dose-dependent antiproliferative effect on the human melanoma cell line A375 [107]. The antiproliferative action, as demonstrated by them, seems to be linked to both cytotoxic and cytostatic effects, while it is not due to the pro-oxidant activity of the extract. After testing the action of the individual components of the extract, they were able to observe that the anti-proliferative activity most likely derived from the extracted set, with multifactorial effects of its components. Furthermore, the proteomic analysis showed that protein levels crucial for the maintenance of cell homeostasis are reduced [107]. In other work, the inhibition of growth against two human melanoma cell lines, M14 and A375, was evaluated. The authors have demonstrated that the extract provoked a remarkable reduction of the growth of both melanoma cell lines with apoptotic cell demise [113].

1.5.2. Zingiber Officinale

Zingiber officinale, ginger, is an herb, whose the rhizome is commonly used as a spice.

Ginger is widely used from centuries for medicinal purpose thanks to the myriad of its properties, such as digestive, carminative, antitussive, appetizer, laxative and others. Ginger has also anti-oxidant, anti-inflammatory and anticarcinogenic properties [117,118]. Gingerols, the main constituents of ginger, are responsible of its pungent taste and are endowed with physiological effects like anti-bacterial, antipyretic and analgesic effects *in vitro* and *in vivo* models [119]. Gingerols are also associated with potent anti-inflammatory and anti-oxidant properties [120]. The effects of ginger extracts are mainly attributed in particular to [6]-gingerol, a phenolic ketone, to which the major effects of ginger extract are attributed. Different studies have demonstrated the chemopreventive effect of ginger extract and its ability to inhibit cell proliferation in human cancer cells by the induction of apoptosis mechanism and caspase-3 activation [121]. Moreover, [6]-gingerol has shown an anti-angiogenic effect *in vitro* and *in vivo* models through the inhibition of VEGF and bFGF causing cell cycle arrest [122]. Many works described the effects of ginger extracts or [6]-gingerol in skin cancer (NMSC and MM models), which are mediated by the modulation of multiple pathways. Davies *et al.* have investigated the role of [6]-gingerol in the inhibition of AP-1 transcriptional complex in HaCaT cells and HaCaT cell clone II-3 (mutant c-Ha-ras-transfected) [123]. Nigam *et al.* have demonstrated the inhibition of growth mediated by [6]-gingerol in A431 cells [124]. Moreover, Cojocaru *et al.* have investigated the cytotoxic activity of ginger extract in amelanotic melanoma cells (amelanotic melanoma is a type of skin melanoma with low pigmentation) in comparison with normal skin fibroblasts. They showed that fresh ginger extract decreased the viability of C32 cells after 24 hours of incubation in a dose-dependent manner without any effect in normal cell viability [125].

1.5.3. Calendula officinalis

Calendula officinalis is an annual herb, normally known as marigold and widely diffused in Mediterranean Countries. Anti-inflammatory, anti-oxidant, anti-bacterial, anti-viral, anti-pyretic properties are attributed to extracts, tinctures and decoctions of marigold flowers. Moreover, from centuries, the extracts of marigold flowers are widely used for the

treatment of skin disorders such as burns, skin wounds, bruises and eczema. These uses are widely reported in the literature [126,127]. It has been demonstrated that the marigold extract exhibited also anti-tumour, cytotoxic and anti-metastatic properties in a variety of human and murine cells line, and protective effects against oxidative stress in human skin cell model [128,129]. These properties are associated to the presence of terpenoids and polyphenolic components in marigold extracts such as rutin, apigenin, luteolin, quercetin and narcissin. Preethi *et al*., in their study, considered the anti-metastatic activity of marigold extract in melanoma cells B16F-10, which are highly metastatic cells that form colonies of cancer cells in the lungs [130]. *In vitro* and subsequently *in vivo* studies have demonstrated the antimetastatic properties of marigold extract [130]. According to their studies marigold extracts are capable to inhibit the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 and GM-CSF, in metastatic lung cells. The extract also determined a decrease in the serum VEGF level [130]. Sak *et al*. have described a cytotoxic activity of the extract on melanoma SK-MEL-2 cells, which however is weaker than that reported on melanoma B16F-10 cells [128]. Regarding NMSC, there is poor information about the activity of marigold flowers. Sak *et al*. have reported the anti-tumour activity in epidermoid carcinoma KB cells [128]. However, there is an interesting study regarding the protective effect of marigold extracts against UVB radiation induced oxidative stress in hairless mice. With this study Fonseca *et al*. have suggested the potential activity of marigold extracts to prevent UVB-induced oxidative damage in skin and its capability to induce healing of damaged skin [126].

1.5.4. Matricaria chamomilla

Chamomile (*Matricaria chamomilla* L. or *Matricaria recutita* L.) is an annual herbaceous plant native to Europe and used in different kind of commercial products (soaps, lotions).

It is well known that chamomile flowers have important anti-inflammatory and antioxidant properties as well as radical scavenging activity. Furthermore the chamomile tea (infusions or decoctions of flowers) is used, from centuries, to treat anxiety, insomnia and other disorders [131]. Many reports described that extract and tea of chamomile flowers are endowed with anti-proliferative activity against different kind of human cells lines through the inhibition of cells growth and the induction of apoptosis [132,133]. Moreover, chamomile extracts and tea are able to inhibit the COX-2 activity implicated in process like carcinogenesis and inflammation. The main properties of chamomile extract or tea are due to the presence of polyphenols, in particular flavonoids (such as apigenin, luteolin, quercetin, patuleitin) and hydroxycinnamic acids (such as ferulic acid). The major polyphenolic constituent of chamomile extract or tea is represented by apigenin which exerts many health beneficial activities (antioxidant, anti-inflammatory and antiproliferative) widely demonstrated [134]. Another traditional use of chamomile tea during centuries has been for the treatment of skin diseases (infections or inflammations like psoriasis, eczema and acne) [135]. Sak *et al*. have reported the cytotoxic activity of chamomile extract both in MM and NMSC, in particular in human MM, SK-MEL-2 and oral epidermoid carcinoma KB cells [128]. Matić *et al*. have demonstrated the cytotoxic action of chamomile tea in human MM Fem-x cells [132]. The cytotoxic activity of chamomile extract results weaker when compared with other extract, as for example marigold extract [128,132]. Nowadays more information about the effect of chamomile extract against skin cancer are required.

1.5.5. Extra-virgin olive oil

A rich source of phenolic compounds (40–1,000 mg/kg) is the extra-virgin olive oil (EVOO), which mainly contains simple phenols, such as tyrosol and hydroxytyrosol, and secoiridoid derivatives, such as oleocanthal and oleacein. Among these, oleocanthal and oleacein are present in larger amounts and play important roles in human health. It has been reported that EVOO phenols show strong antioxidants proprieties and also others potent biological activities, including anti-inflammatory, immune-modulatory, antimicrobial, metabolic and anticancer activity, in *in vivo* and *in vitro* models [136,137]. To confirm this, the consummation of EVOO has been largely associated to health effects of the Mediterranean diet [138,139]. More than 30 phenolic compounds have been identified in EVOO [140] and an increasing number of manuscripts highlight the photo-protective, anti-inflammatory, immune-modulatory and anti-tumor effects of some polyphenols in skin cancer [141] but not all of them were currently tested in models of skin cancers.

Recently, our research group studied, in *in vitro* NMSC models, chemopreventive and anticancer properties of two different EVOO extracts with high content of secoiridoid derivatives and of the isolated secoiridoid compounds (oleocanthal and oleacein) [142]. It was found that in A431 cells, EVOO extracts decreased cell viability in a concentration-dependent manner, reduced migration and prevented colony and spheroid formation. As concern, the mechanism of action the two extracts decreased B-Raf levels by about 80-95%, p-Akt levels by 40-50%, and p-Erk expression by about 35-50%. Oleocanthal and oleacein decreased cell viability in a concentration-dependent manner in A431 cells, in particular oleacein that shown the best activity. Moreover, it was shown that oleocanthal and oleacein were able to induce pro-apoptotic effects and to inhibit B-Raf-Erk pathway [142].

Furthermore, the chemoprevention effect of extracts and secoiridoids was evaluated on immortalized HaCaT stimulated with EGF, an *in vitro* model reproducing the progression from actinic keratosis to cutaneous SCC. In this model, extracts displayed a concentration-dependent decrease of cell viability, reducing of B-Raf expression, and phosphorylation of Erk 1/2 and Akt. Relative to the single compounds, oleocanthal resulted more active then oleacein to inhibit cell growth [142].

It is interesting to note that in this work, for the first time, the *in vitro* ability of oleacein, to induce apoptosis in SCC cells inhibiting key signalling pathway, was proved [142].

We, also, reported that oleocanthal has cytotoxic activity against the human MM cells, A375 and 501Mel, with no effect on normal cells. Oleocanthal inhibits ERK1/2 and AKT phosphorylation and down-regulates Bcl-2 expression.

Table 2 Effects of phytoextracts in NMSC and MM.

Phytoextract	Phenols/Polyphenols	Biological Process	Models	References
Rosmarinus officinalis	rosmarinic acid, carnosol and carnosic acid apigenin, luteolin, caffeic acid and scutellarin	⇓ Cell proliferation ⇓ Cell growth ⇑ Apoptosis	A375 M14 A375	107 113
Zingiber officinale	Gingerols ([6]-gingerol)	⇓ Cell invasion ⇓ Cell growth ⇓ Cell viability	HaCaT cell clone II-3 A431 C32	123 124 125
Calendula officinalis	rutin, apigenin, luteolin, quercetin and narcissin	Prevenction oxidative damage Cytotoxic activity Anti-tumor activity ⇓ Metastasis	Hairless mice+UVB SK-MEL-2 BF16F10 oral epidermoid carcinoma KB cells B16F-10 C57BL/6 mice	126 128 128 130
Matricaria chamomilla	apigenin, luteolin, quercetin, patuleitin ferulic acid.	Cytotoxic activity Cytotoxic activity	SK-MEL-2 oral epidermoid carcinoma KB human MM Fem-x cells	128 132
Extra-virgin olive oil	tyrosol hydroxytyrosol oleocanthal oleacein	⇓ Cell viability ⇓ Cell migration ⇑ Apoptosis Prevenction colony and spheroid formation ⇓ Cell viability ⇓ Cell growth ⇓ Cell viability No effect	A431 HaCaT + EGF A375 501Mel Normal Cells	142 142 142 142

0929-8673/19 $58.00+.00

CONCLUSION

In the recent years, the beneficial effects of natural compounds have emerged, confirming that the use of dietary phytochemicals may be an attractive option for the prevention and/or treatment of cutaneous diseases including skin cancer. The studies reported here strongly underline the efficacy of polyphenols in chemoprevention and treatment of NMSC and MM, representing the next step to improve management of the patients.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, including financial and material support for work in this manuscript.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Montes de Oca, M.K.; Pearlman, R.L.; McClees, S.F.; Strickland, R.; Afaq, F. Phytochemicals for the prevention of photocarcinogenesis. *Photochem. Photobiol.,* **2017,** *93*, 956-974.

[2] D'Orazio, J.; Jarrett, S.; Amaro-Ortiz, A.; Scott, T. UV radiation and the skin. *Int. J. Mol. Sci.,* **2013,** *14*, 12222-12248.

[3] Brash, D.E.; Rudolph, J.A.; Simon, J.A.; Lin, A.; McKenna, G.J.; Baden, H.P.; Halperin, A.J.; Ponten, J. A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. *Proc. Natl. Acad. Sci. U.S.A.,* **1991,** *88*, 10124–10128.

[4] Matsumura, Y.; Ananthaswamy, H.N. Toxic effects of ultraviolet radiation on the skin. *Toxicol. Appl. Pharmacol.,* **2004,** *195*, 298–308.

[5] Clingen, P.H.; Arlett, C.F.; Roza, L.; Mori, T.; Nikaido, O.; Green, M.H. Induction of cyclobutane pyrimidine dimers, pyrimidine(6-4)pyrimidone photoproducts, and Dewar valence isomers by natural sunlight in normal human mononuclear cells. *Cancer Res.,* **1995,** *55*, 2245–2248.

[6] Rastogi, R.P.; Richa; Kumar, A.; Tyagi, M.B.; Sinha, R.P. Molecular Mechanisms of Ultraviolet Radiation-Induced DNA Damage and Repair. *J. Nucleic. Acids.,* **2010,** *2010*, 592980.

[7] Ljungman, M.; Zhang, F. Blockage of RNA polymerase as a possible trigger for UV light-induced apoptosis. *Oncogene,* **1996,** *13*, 823–831.

[8] Prasad, S.; Gupta, S.C.; Tyagi, A.K. Reactive oxygen species (ROS) and cancer: Role of antioxidative nutraceuticals. *Cancer Lett.,* **2017,** *387*, 95–105.

[9] Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics. *CA Cancer. J. Clin.,* **2017***, 67*, 7−30.

[10] Miller, K.D.; Nogueira, L.; Mariotto, A.B.; Rowland, J.H.; Yabroff, K.R.; Alfano, C.M.; Jemal, A.; Kramer, J.L.; Siegel, R.L. Cancer Treatment and SurvivorshipStatistics, 2019. *CA Cancer J. Clin.,* **2019,** *69*, 363–385.

[11] Berger, M.F.; Hodis, E.; Heffernan, T.P.; Deribe, Y.L.; Lawrence, M.S.; Protopopov, A.; Ivanova, E.; Watson, I.R.; Nickerson, E.; Ghosh, P.; Zhang, H.; Zeid, R.; Ren, X.; Cibulskis, K.; Sivachenko, A.Y.; Wagle, N.; Sucker, A.; Sougnez, C.; Onofrio, R.; Ambrogio, L.; Auclair, D.; Fennell, T.; Carter, S.L.; Drier, Y.; Stojanov, P.; Singer, M.A.; Voet, D.; Jing, R.; Saksena, G.; Barretina, J.; Ramos, A.H.; Pugh, T.J.; Stransky, N.; Parkin, M.; Winckler, W.; Mahan, S.; Ardlie, K.; Baldwin, J.; Wargo, J.; Schadendorf, D.; Meyerson, M.; Gabriel, S.B.; Golub, T.R.; Wagner, S.N.; Lander, E.S.; Getz, G.; Chin, L.; Garrawa, L.A. Melanoma genome sequencing reveals frequent PREX2 mutations. *Nature,* **2012,** *485*, 502−06.

[12] Kennedy, C.; ter Huurne, J.; Berkhout, M.; Gruis, N.; Bastiaens, M.; Bergman, W.; Willemze, R.; Bavinck, J. N. Melanocortin 1 Receptor (MC1R) Gene Variants Are Associated With an Increased Risk for Cutaneous Melanoma Which Is Largely Independent of Skin Type and Hair Color. *J. Invest. Dermatol.,* **2001,** *117*, 294-300.

[13] Shain, A.H.; Yeh, I.; Kovalyshyn, I.; Sriharan, A.; Talevich, E.; Gagnon, A.; Dummer, R.; North, J.; Pincus, L.; Ruben, B.; Rickaby, W.; D'Arrigo, C.; Robson, A.; Bastian, B.C. The Genetic Evolution of Melanoma From Precursor Lesions. *N. Engl. J. Med.,* **2015,** *373*, 1926-36.

[14] Samarasinghe, V.; Madan, V. Nonmelanoma Skin Cancer. *J. Cutan. Aesthet. Surg.,* **2012,** *5*, 3–10.

[15] Haque, T; Rahman, K.M.; Thurston, D.E.; Hadgraft, J.; Lane, M.E. Topical therapies for skin cancer and actinic keratosis. *Eur. J. Pharm. Sci.,* **2015,** *77*, 279-289.

[16] Bertozzi, N.; Simonacci, F.; Pio Grieco, M.; Grignaffini, E.; Raposio, E., Single center evidence for the treatment of basal cell carcinoma of the head and neck. *Acta Biomed.,* **2019,** *90*, 77–82.

[17] Bowden, G.T. Prevention of non-melanoma skin cancer by targeting ultraviolet-B-light signalling. *Nat. Rev. Cancer,* **2004,** *4*, 23–35

[18] Farage M.A.; Miller K.W.; Elsner P.; Maibach H.I. Intrinsic and extrinsic factors in skin ageing: a review. *Int. J. Cosmet. Sci.,* **2008,** *30*, 87–95.

[19] Schieber, M.; Chandel, N.S. ROS function in redox signaling and oxidative stress. *Curr Biol.,* **2014,** *24*, R453-62.

[20] Moldogazieva, N.T.; Mokhosoev, I.M.; Feldman, N.B.; Lutsenko, S.V. ROS and RNS signalling: adaptive redox switches through oxidative/nitrosative protein modifications. *Free Radic. Res.,* **2018,** *52*, 507–543.

[21] Guzik, T.J.; West, N.E.; Pillai, R.; Taggart, D.P.; Channon, K.M. Nitric oxide modulates superoxide release and peroxynitrite formation in human blood vessels. *Hypertension,* **2002,** *39*, 1088–1094.

[22] Bickers, D.R.; Athar, M. Oxidative Stress in the Pathogenesis of Skin Disease. *J. Invest. Dermatol.,* **2006,** *126*, 2565–2575.

[23] De Gruijl, F.R. Photocarcinogenesis: UVA vs UVB. *Methods Enzymol.,* **2000,** *319*, 359-66.

[24] Dhar, A.; Young, M.R.; Colburn, N.H. The role of AP-1, NF-kappaB and ROS/NOS in skin carcinogenesis: the JB6 model is predictive. *Mol. Cell. Biochem.,* **2002,** *185*, 234–235.

[25] Fischer, S.M.; Pavone, A.; Mikulec, C.; Langenbach, R.; Rundhaug, J. E. Cyclooxygenase-2 expression is critical for chronic UV-induced murine skin carcinogenesis. *Mol. Carcinog.,* **2007,** *46*, 363–371.

[26] Kim, S.Y.; Kim, D.S.; Kwon, S.B.; Park, E.S.; Huh, C.H.; Youn, S.W.; Kim, S.W.; Park, K.C. Protective effects of EGCG on UVB-induced damage in living skin equivalents. *Arch. Pharm. Res.,* **2005,** *28*, 784–790.

[27] Elmets, C.A.; Ledet, J.J.; Athar, M., Cyclooxygenases: mediators of UV-induced skin cancer and potential targets for prevention. *J. Invest. Dermatol.,* **2014,** *134*, 2497–2502.

[28] Hirota, A.; Kawachi, Y.; Itoh, K.; Nakamura, Y.; Xu, X.; Banno, T.; Takahashi, T.; Yamamoto, M.; Otsuka, F. Ultraviolet A irradiation induces NF-E2-related factor-2 activation in dermal fibroblasts: protective role in UVA-induced apoptosis. *J. Invest. Dermatol.,* **2005,** *124*, 825–832.

[29] Surh, Y.J. Cancer chemoprevention with dietary phytochemicals. *Nat. Rev. Cancer,* **2003,** *3*, 768–780.

[30] Trachootham, D.; Lu, W.; Ogasawara, M. A.; Rivera-Del Valle, N.; Huang, P., Redox Regulation of Cell Survival. *Antioxid. Redox Signal.,* **2008,** *10*, 1343–1374.

[31] Nandakumar, V.; Vaid, M.; Tollefsbol, T.O.; Katiyar, S.K. Aberrant DNA hypermethylation patterns lead to transcriptional silencing of tumor suppressor genes in UVB-exposed skin and UVB-induced skin tumors of mice. *Carcinogenesis,* **2011,** *32*, 597-604.

[32] Sander, C.S.; Chang, H.; Salzmann, S.; Müller, C.S.; Ekanayake-Mudiyanselage, S.; Elsner, P.; Thiele, J.J. Photoaging is associated with protein oxidation in human skin in vivo. *J. Invest. Dermatol.*, **2002,** *118*, 618-25.

[33] Leccia, M.T.; Yaar, M.; Allen, N.; Beani, J.C. Solar simulated irradiation modulates gene expression and activity of antioxidant enzymes in cultured human dermal fibroblasts. *Exp. Dermatol.,* **2001,** *10*, 272–9.

[34] Sander, C.S.; Hamm, F.; Elsner, P.; Thiele, J.J. Oxidative stress in malignant melanoma and non-melanoma skin cancer. *Br. J. Dermatol.,* **2003,** *148*, 913–922.

[35] Pandel, R.; Poljŝak, B.; Godic, A.; Dahmane, R. Skin photoaging and the role of antioxidants in its prevention. *ISRN Dermatology,* **2013,** *Article ID 930164*, 11 pages.

[36] Poljŝak, B.; Dahmane, R.; Godic, A. Skin and antioxidants. *J. Cosmet. Laser Ther.,* **2013,** *15*, 107–113.

[37] Khan, N.; Afaq, F.; Mukhtar, H. Cancer chemoprevention through dietary antioxidants: progress and promise. *Antioxid. Redox Signal.,* **2008,** *10*, 475–510.

[38] Katiyar, S.K.; Perez, A.; Mukhtar, H. Green tea polyphenol treatment to human skin prevents formation of ultraviolet light B-induced pyrimidine dimers in DNA. *Clin. Cancer Res.,* **2000,** *6*, 3864–3869.

[39] Katiyar, S.K.; Mukhtar, H. Green tea polyphenol (-)-epigallocatechin-3-gallate treatment to mouse skin prevents UVB-induced infiltration of leukocytes, depletion of antigen-presenting cells, and oxidative stress. *J. Leukoc. Biol.,* **2001,** *69,* 719-26.

[40] Meeran, S.M.; Mantena, S.K.; Elmets, C.A.; Katiyar, S.K. (−)-Epigallocatechin-3-gallate prevents photocarcinogenesis in mice through interleukin-12-dependent DNA repair. *Cancer Res.,* **2006,** *66*, 5512–5520.

[41] Singh, T.; Katiyar, S.K. Green tea polyphenol, (-)-epigallocatechin-3-gallate, induces toxicity in human skin cancer cells by targeting beta-catenin signaling. *Toxicol. Appl. Pharmacol.,* **2013,** *273*, 418-424.

[42] Nandakumar, V.; Vaid, M.; Katiyar, S.K. (-)-Epigallocatechin-3-gallate reactivates silenced tumor suppressor genes, Cip1/p21 and p16INK4a, by reducing DNA methylation and increasing histones acetylation in human skin cancer cells. *Carcinogenesis.* **2011,** *32*, 537-44.

[43] Kato, K.; Long, N.K.; Makita, H.; Toida, M.; Yamashita, T.; Hatakeyama, D.; Hara, A.; Mori, H.; Shibata, T. Effects of green tea polyphenol on methylation status of RECK gene and cancer cell invasion in oral squamous cell carcinoma cells. *Br. J. Cancer,* **2008** *99*, 647-54.

[44] Bae, J.Y.; Choi, J.S.; Choi, Y.J.; Shin, S.Y.; Kang, S.W.; Han, S.J.; Kang, Y.H. (−) Epigallocatechin gallate hampers collagen destruction and collagenase activation in ultraviolet-B-irradiated human dermal fibroblasts: involvement of mitogen-activated protein kinase. *Food Chem. Toxicol.,* **2008,** *46*, 1298– 1307.

45] Kim, A.L.; Labasi, J.M.; Zhu, Y.; Tang, X.; McClure, K.; Gabel, C.A.; Athar, M.; Bickers, D.R. Role of p38 MAPK in UVB-induced inflammatory responses in the skin of SKH-1 hairless mice. *J. Invest. Dermatol.,* **2005,** *124*, 1318–25.

[46] Lu, Y.P.; Lou, Y.R.; Xie, J.G.; Peng, Q.Y.; Liao, J.; Yang, C.S.; Huang, M.T.; Conney, A.H. Topical

applications of caffeine or (−)-epigallocatechin gallate (EGCG) inhibit carcinogenesis and selectively increase apoptosis in UVB-induced skin tumors in mice. *Proc. Natl. Acad. Sci USA,* **2002,** *99*, 12455–12460.

[47] Katiyar, S.K.; Matsui, M.S.; Elmets, C.A.; Mukhtar, H. Polyphenolic antioxidant (−)-epigallocatechin-3-gallate from green tea reduces UVB-induced inflammatory responses and infiltration of leukocytes in human skin. *Photochem. Photobiol.,* **1999,** *69*, 148–153.

[48] Linden, K.G.; Carpenter, P.M.; McLaren, C.E.; Barr, R.J.; Hite, P.; Sun, J.D.; Li, K.T.; Viner, J.L.; Meyskens, F.L. Chemoprevention of nonmelanoma skin cancer: experience with a polyphenol from green tea. *Recent Results Cancer Res.,* **2003,** *163*, 165-71.

[49] Sevın, A.; Özta, P.; Senen, D.; Han, U.; Karaman, C.; Tarimci, N.; Kartal, M.; Erdogan, B. Effects of polyphenols on skin damage due to ultraviolet A rays: An experimental study on rats. *J. Eur. Acad. Dermatol. Venereol.,* **2007,** *21*, 650–656.

[50] Zhang, J.; Lei, Z.; Huang, Z.; Xu, Z.; Zhou, Y.; Luo, Z.; Zeng, W.; Su, J.; Peng, C.; Chen, X. Epigallocatechin-3-gallate(EPIGALLOCATCHIN-3-GALLATE) suppresses MM cell growth and metastasis by targeting TRAF6 activity. *Oncotarget,* **2016,** *7*, 79557–79571.

[51] Nihal, M.; Roelke, C.T.; Wood, G.S. Anti-MM Effects of Vorinostat in Combination with Polyphenolic Antioxidant (−)-Epigallocatechin-3- Gallate (EGCG). *Pharm. Res.,* **2010,** *27*, 1103–1114.

[52] Maheshwari, R.K.; Singh, A.K.; Gaddipati, J.; Srimal, R.C. Multiple biological activities of curcumin: a short review. *Life Sci.,* **2006,** *78*, 2081–7.

[53] Qiu, Y.; Yu, T.; Wang, W.; Pan, K.; Shi, D.; Sun, H. Curcumin-induced MM cell death is associated with mitochondrial permeability transition pore (mPTP) opening. *Biochem. Bioph. Res. Co.,* **2014,** *448*, 15–21.

[54] Wu, J.; Lu, W-Y.; Cui, L.-L. Inhibitory Effect of Curcumin on Invasion of Skin Squamous Cell Carcinoma A431 Cells. *Asian Pac. J. Cancer Prev.,* **2015,** *16*, 2813-2818.

[55] Sonavane, K.; Phillips, J.; Ekshyyan, O.; Moore-Medlin, T.; Roberts, G.J.; Rong, X.; Lakshmaiah, R.R.; Abreo, F.; Boudreaux, D.; Clifford, J.L.; Nathan, C.A.O. Topical Curcumin-Based Cream Is Equivalent to Dietary Curcumin in a Skin Cancer Model. *J. Skin Cancer.,* **2012,** *2012*, 147863.

[56] Tsai, K.-D.; Lin, J.-C.; Yang, S.-M.; Tseng, M.-J.; Hsu, J.-D.; Lee, Y.-J.; Cherng, J.-M. Curcumin Protects against UVB-Induced Skin Cancers in SKH-1 HairlessMouse: Analysis of Early Molecular Markers in Carcinogenesis. *Evid.-based Complementary Altern. Med.,* **2012**, 1-11.

[57] Odot, J.; Albert, P.; Carlier, A.; Tarpin, M.; Devy, J.; Madoulet, C. In vitro and in vivo anti-tumoral effect of curcumin against MM cells. *Int. J. Cancer,.* **2004,** *111*, 381–387.

[58] Yu, T.; Ji, J.; Guo, Y.L. MST1 activation by curcumin mediates JNK activation, Foxo3a nuclear translocation and apoptosis in MM cells. *Biochem. Biophys. Res. Commun.,* **2013,** *441*, 53–58.

[59] Jason, A.; Bush, K.-J.J.; Cheung, J.; Gang, L. Curcumin Induces Apoptosis in Human MM Cells through a Fas Receptor/Caspase-8 Pathway Independent of p53. *Experimental Cell. Research,* **2001,** *271*, 305-314.

[60] Qiu, Y.; Yu, T.; Wang, W.; Pan, K.; Shi, D.; Sun, H. Curcumin-induced MM cell death is associated with mitochondrial permeability transition pore (mPTP) opening *Biochem. Bioph. Res. Co.,* **2014,** *448* 15–21.

[61] Vitale, N.; Kisslinger, A.; Paladino, S.; Procaccini, C.; Matarese, G.; Pierantoni, G.M.; Mancini, F.P.; Tramontano, D. Resveratrol couples apoptosis with autophagy in UVB-irradiated HaCaT cells. *PLoS ONE,* **2013,** *8*, e80728.

[62] Back, J.H.; Zhu, Y.; Calabro, A.; Queenan, C.; Kim, A.S.; Arbesman, J.; Kim, A. Resveratrol-Mediated Downregulation of Rictor Attenuates Autophagic Process and Suppresses UV-Induced Skin Carcinogenesis. *Photochem. Photobiol.,* **2012,** *88*, 1165-1172.

[63] Hao, Y.; Huang, W.; Liao, M.; Zhu, Y.; Liu, H.; Hao, C.; Liu, G.; Zhang, G.; Feng, H.; Ning, X.; Li, H.; Li Z. The inhibition of resveratrol to human skin squamous cell carcinoma A431 xenografts in nude mice. *Fitoterapia,* **2013,** *86*, 84–91.

[64] Niles, R.M.; McFarland, M.; Weimer, M.B.; Redkar, A.; Fu, Y.M.; Meadows, G.G. Resveratrol is a potent inducer of apoptosis in human MM cells. *Cancer Lett.,* **2003,** *190,* 157–163.

[65] Gatouillat, G.; Balasse, E.; Joseph-Pietras, D.; Morjani, H.; Madoulet, C. Resveratrol induces cell-cycle disruption and apoptosis in chemoresistant B16 MM. *J. Cell. Biochem.,* **2010,** *110*, 893–902.

[66] Bhattacharya, S.; Darjatmoko, S.R.; Polans, A.S. Resveratrol Modulates the Malignant Properties of Cutaneous MM via Changes in the Activation and Attenuation of the Anti-apoptotic Proto-oncogenic Protein Akt/PKB. *MM Res.,* **2011,** *21*, 180–187.

[67] Tong, L.; Wu, S. The Mechanisms of Carnosol in Chemoprevention of Ultraviolet B-Light-Induced Non-Melanoma Skin Cancer Formation. *Sci. Rep.,* **2018,** *8*, 1-9.

[68] Tong, L.; Wu, S. The role of constitutive nitric-oxide synthase in ultraviolet B light-induced nuclear factor kappaB activity. *J. biol. chem.,* **2014,** *289*, 26658–26668.

[69] Choi, S. M.; Kim, D. H.; Chun, K. S.; Choi, J.S. Carnosol induces apoptotic cell death through ROS-dependent inactivation of STAT3 in human MM G361 cells. *Appl. Biol. Chem.,* **2019,** *62*, 55.

[70] Alcaraz, M.; Achel, D.G.; Olivares, A.; Olmos, E.; Alcaraz-Saura, M.; Castillo, J. Carnosol, radiation and MM: A translational possibility. *Clin. Transl. Oncol.,* **2013,** *15*, 712-719.

[71] Huang, S.C.; Ho, C.T.; Lin-Shiau, S.Y.; Lin, J.K. Carnosol inhibits the invasion of B16/F10 mouse MM cells by suppressing metalloproteinase-9 through down-regulating nuclear factorkappa B and c-Jun. *Biochem. Pharmacol.,* **2005,** *69*, 221-232.

[72] Ha, S.J.; Lee, J.; Park, J.; Kim, Y.H.; Lee, N.H.; Kim, Y.E.; Song, K.; Chang, P.; Jeonge, C.; Junga, S.K. Syringic acid prevents skin carcinogenesis via regulation of NoX and EGFR signaling. *Biochem. Pharmacol.,* **2018,** *154*, 435–445.

[73] Xu, Y.; Tan, L.; Grachtchouk, V.; Voorhees, J.J.; Fisher, G.J. Receptor-type Protein-tyrosine Phosphatase-k Regulates Epidermal Growth Factor Receptor Function. *J. Biol. Chem.,* **2005,** *280*, 42694–42700.

[74] Paulsen, C.E.; Truong, T.H.; Garcia, F.J.; Homann, A.; Gupta, V.; Leonard, S. E.; Carroll, K.S. Peroxide-dependent sulfenylation of the EGFR catalytic site enhances kinase activity. *Nat. Chem. Biol.,* **2012,** *8*, 57–64.

[75] Balupillai, A.; Nagarajan, R.P.; Ramasamy, K.; Govindasamy, K.; Muthusamy, G. Caffeic acid prevents UVB radiation induced photocarcinogenesis through regulation of PTEN signaling in human dermal fibroblasts and mouse skin. *Toxicol. Appl. Pharmacol.,* **2018,** *352*, 87–96.

[76] Ming, M.; Feng, L.; Shea, C.R.; Soltani K.; Zhao B.; Han W.; Smart R.C.; Trempus C.S.; He Y-Y. PTEN Positively Regulates UVB-Induced DNA Damage Repair. *Cancer Res.,* **2011,** *71*, 5287–5295.

[77] Di Cristofano, A.; Pandolfi, P.P. The multiple roles of PTEN in tumor suppression. *Cell,* **2000,** *100*, 387–390.

[78] Balupillai, A.; Prasad, R.N.; Ramasamy, K.; Muthusamy, G.; Shanmugham, M.; Govindasamy, K.; Gunaseelan, S. Caffeic Acid Inhibits UVB-induced Inflammation and Photocarcinogenesis Through Activation of Peroxisome Proliferator-activated Receptor-γ in Mouse Skin. *Photochem. Photobiol.,* **2015,** *91*, 1458-68.

[79] Agilan, B.; Prasad, N.R.; Kanimozhi, G.; Karthikeyan, R.; Ganesan, M.; Mohana, S.; Velmurugan, D.; Ananthakrishnan, D. Caffeic Acid Inhibits Chronic UVB-Induced Cellular Proliferation Through JAK-STAT3 Signaling in Mouse Skin. *Photochem. Photobiol.,* **2016** *92*, 467-74.

[80] Yang, Y.; Li, Y.; Wang, K.; Wang, Y.; Yin, W.; Li, L. p38/NF-kB/snail pathway is involved in caffeic acid-induced inhibition of cancer stem cells-like properties and migratory capacity in malignant human keratinocyte. *PLoS One,* **2013,** *8*, e58915.

[81] Pluemsamran, T.; Onkoksoong, T.; Panich, U. Caffeic Acid and Ferulic Acid Inhibit UVA-Induced Matrix Metalloproteinase-1 through Regulation of Antioxidant Defense System in Keratinocyte HaCaT Cells. *Photochem. Photobiol.,* **2012,** *88*, 961–968.

[82] Pelinson, L.P.; Assmann, C.E.; Palma, T.V.; da Cruz, I.; Pillat, M.M.; Mânica, A.; Stefanello, N.; Weis, G.C.C.; de Oliveira Alves, A.; de Andrade, C. M.; Ulrich, H.; Morsch, V.M.M.; Schetinger, M.R.C.; Bagatini, M.D. Antiproliferative and apoptotic effects of caffeic acid on SK-Mel-28 human MM cancer cells. *Mol. Bio. Rep.,* **2019,** *46*, 2085–2092.

[83] Tee-ngam, P.; Nunant, N.; Rattanarat, P.; Siang- proh, W.; Chailapakul, O. Simple and rapid de- termination of ferulic acid levels in food and cosmetic samples using paper-based plat- forms. *Sensors,* **2013,** *13*, 13039–13053.

[84] Lodovici, M.; Guglielmi, F.; Meoni, M.; Dolara, P. Effect of natural phenolic acids on DNA oxi- dation in vitro. *Food Chem. Toxicol.,* **2001,** *39*, 1205–1210.

[85] Yang, G.W.; Jiang, J.S.; Lu, W.Q. Ferulic Acid Exerts Anti-Angiogenic and Anti-Tumor Activity by Targeting Fibroblast Growth Factor Receptor 1-Mediated Angiogenesis. *Int. J. Mol. Sci.,* **2015,** *16*, 24011-24031.

[86] Ceci, C.; Lacal, P.M.; Tentori, L.; De Martino, M.G.; Miano, R.; Graziani, G. Experimental Evidence of the Antitumor, Antimetastatic and Antiangiogenic Activity of Ellagic Acid. *Nutrients,* **2018,** *10*, 1-23.

[87] Hseu, Y.C.; Chou, C.W.; Kumar, K.J.S.; Fu, K.T.; Wang, H.M.; Hsu, L.S., Kuo Y.H.; Wu C.R.; Chen S.C.; Yang, H.L. Ellagic acid protects human keratinocyte (HaCaT) cells against UVA-induced oxidative stress and apoptosis through the upregulation of the HO-1 and Nrf-2 antioxidant genes. *Food Chem. Toxicol.,* **2012,** *50*, 1245–1255.

[88] Lembo, S.; Balato, A.; Di Caprio, R.; Cirillo, T.; Giannini, V.; Gasparri, F.; Monfrecola, G. The modulatory effect of ellagic acid and rosmarinic acid on ultraviolet-B-induced cytokine/chemokine gene expression in skin keratinocyte (HaCaT) cells. *Biomed. Res. Int.,* **2014**, *2014, ID 346793.*

[89] Jensen, J.D.; Dunn, J.H.; Luo, Y.; Liu, W.; Fujita, M.; Dellavalle, R.P. Ellagic acid inhibits MM growth in vitro. *Dermatol. Reports,* **2011,** *3*, e36

[90] Vostalova, J.; Zdarilova, A.; Svobodova, A., Prunellavulgaris extract and rosmarinic acid prevent UVB induced DNA damage and oxidative stress in HaCaT keratinocytes. *Arch. Dermatol. Res.,* **2010,** *302*, 171–181.

[91] Lee, H.J.; Cho, H.S.; Park, E.; Kim, S.; Lee, S. Y.; Kim, C.S., Rosmarinic acid protects human dopaminergic neuronal cells against hydrogen peroxide-induced apoptosis. *Toxicology,* **2008,** *250*, 109-115.

[92] Beauchamp, G.K.; Keast, R.S.; Morel, D.; Lin, J.; Pika, J.; Han, Q.; Lee, C.H.; Smith, A.B.; Breslin, P.A. Phytochemistry: ibuprofen-like activity in extra-virgin olive oil. *Nature,* **2005,** *437*, 45-6.

[93] Fernando, P.M.D.J.; Piao, M.J.; Kang, K.A.; Ryu, Y.S.; Hewage, S.R.K.M.; Chae, S.W.; Hyun, J.W. Rosmarinic Acid Attenuates Cell Damage against UVB Radiation-Induced Oxidative Stress via Enhancing Antioxidant Effects in Human HaCaT Cells. *Biomol. Ther.,* **2016,** *24*, 75-84

[94] Bashir, M.M.; Sharma, M.R.; Werth, V.P. UVB and proinflammatory cytokines synergistically activate TNF-. *J. Invest. Dermatol.,* **2009,** *129*, 994– 1001.

[95] Verschooten, L.; Smaers, K.; Van Kelst, S.; Proby, C.; Maes, D.; Declercq, L.; Agostinis, P.; Garmyn, M. The flavonoid luteolin increases the resistance of normal, but not malignant keratinocytes, against UVB-induced apoptosis. *J. Invest. Dermatol.,***2010,** *130*, 2277-85.

[96] Byun, S.; Lee, K. W.; Jung, S. K.; Lee, E. J.; Hwang, M. K.; Lim, S. H.; Bode, A. M.; Lee, H. J.; Dong, Z.

Luteolin inhibits protein kinase C(epsilon) and c-Src activities and UVB-induced skin cancer. *Cancer Res.,* **2010** *70*, 2415-23.

[97] Lin, Y.S.; Tsai, P.H.; Kandaswami, C.C.; Cheng, C.H.; Ke, F.C.; Lee, P.P.; Hwang, J.J.; Lee, M.T., Effects of dietary flavonoids, luteolin, and quercetin on the reversal of epithelial-mesenchymal transition in A431 epidermal cancer cells. *Cancer Sci.,* **2011,** *102*, 1829-39.

[98] Yao, X.; Jiang, W.; Yuc, D.; Yan, Z. Luteolin inhibits proliferation and induces apoptosis of human MM cells in vivo and in vitro by suppressing MMP-2 and MMP-9 through the PI3K/AKT pathway. *Food funct.,* **2019,** *10*, 703-712.

[99] Kiraly, A.J.; Soliman, E.; Jenkins, A.; Van Dross, R.T. Apigenin inhibits COX-2, PGE2, and EP1 and also initiates terminal differentiation in the epidermis of tumor bearing mice. *Prostaglandins Leukot. Essent. Fatty Acids,* **2016,** *104*, 44-53.

[100] Paredes-Gonzalez, X.; Fuentes, F.; Su, Z.Y.; Kong, A.N.T. Apigenin Reactivates Nrf2 Anti- oxidative Stress Signaling in Mouse Skin Epidermal JB6 P + Cells Through Epigenetics Modifications. *AAPS J.,* **2014,** *16*, 727-735.

[101] Cao, H.H.; Chu, J.H.; Kwan, H.Y.; Su, T.; Yu, H.; Cheng, C.Y.; Fu, X.Q.; Guo, H.; Li, T.; Tse, A.K.W.; Chou, G.X.; Mo, H.B.; Yu, Z.L. Inhibition of the STAT3 signaling pathway contributes to apigenin-mediated anti-metastatic effect in MM. *Sci. Rep.,* **2016,** *6*, 21731

[102] Hong, S.H.; Cha, H.J.; Hwang-Bo, H.; Kim, M.Y.; Kim, S.Y.; Ji, S.Y.; Cheong, J.; Park, C.; Lee, H.; Kim, G.Y.; Moon, S.; Yun, S.J.; Chang, Y.; Kim, W.; Choi, Y.H. Anti-Proliferative and Pro-Apoptotic Effects of Licochalcone A through ROS-Mediated Cell Cycle Arrest and Apoptosis in Human Bladder Cancer Cells. *Int. J. Mol. Sci.,* **2019** *20*, 3820.

[103] Kang, T.H.; Yoon, G.; Kang, I.A.; Oh, H.N.; Chae, J.; Shim, J.H. Natural Compound Licochalcone B Induced Extrinsic and Intrinsic Apoptosis in Human Skin Melanoma (A375) and Squamous Cell Carcinoma (A431) Cells. *Phytother. Res.,* **2017,** *31*, 1858–1867

[104] Vaid, M.; Sharma, S.D.; Katiyar, S.K. Proanthocyanidins inhibit photocarcinogenesis through enhancement of DNA repair and xeroderma pigmentosum group A-dependent mechanism. *Cancer Prev. Res.,* **2010,** *3*, 1621–1629.

[105] Nirmala, J.G.; Celsia, S.E.; Swaminathan, A.; Narendhirakannan, R.T.; Chatterjee, S. Cytotoxicity and apoptotic cell death induced by Vitis vinifera peel and seed extracts in A431 skin cancer cells. *Cytotechnology,* **2017,** *70*, 537-554.

[106] Vaid, M.; Singh, T.; Prasad, R.; Katiyar, S.K., Bioactive proanthocyanidins inhibit growth and induce apoptosis in human MM cells by decreasing the accumulation of β-catenin. *Int. J. Oncol.,* **2016,** *48*, 624-634.

[107] Cattaneo, L.; Cicconi, R.; Mignogna, G.; Giorgi, A.; Mattei, M.; Graziani, G.; Ferracane, R.; Grosso, A.; Aducci, P.; Schininà, M. E.; Marra, M. Anti-Proliferative Effect of Rosmarinus officinalis L. Extract on Human Melanoma A375 Cells. *PLoS One,* **2015**, *10*, e0132439.

[108] Garbarino, J.A.; Troncoso, N.; Delpiano, P.; Carvajal, L.; Russo, A. Antioxidant Activity Analysis for the Selection of Rosmarinus officinalis L. *Nat. Prod. Commun.,* **2006,** *1*, 1123-1128.

[109] Moore, J.; Yousef, M.; Tsiani, E. Anticancer Effects of Rosemary (Rosmarinus officinalis L.) Extract and Rosemary Extract Polyphenols. *Nutrients*, **2016**, *8*, 731.

[110] Kontogianni, V.G.; Tomic, G.; Nikolic, I.; Nerantzaki, A.A.; Sayyad, N.; Stosic-Grujicic, S.; Stojanovic, I.; Gerothanassis, I.P.; Tzakos, A.G. Phyto-chemical profile of Rosmarinus officinalis and Salvia officinalis extracts and correlation to their antioxi-dant and anti-proliferative activity. *Food Chem. Toxicol.,* **2013,** *136*, 120–9.

[111] Cheung, S.; TaI, J. Anti-proliferative and antioxidant properties of rosemary (Rosmarinus officina- lis). *Oncol. Rep.,* **2007,** *17*, 1525–1531.

[112] Yesil-Celiktas, O.; Sevimli, C.; Bedir, E.; Vardar-Sukan, F. Inhibitory effects of rosemary extracts, carnosic acid and rosmarinic acid on the growth of various human cancer cell lines. *Plant Foods Hum. Nutr.,* **2010,** *65*, 158–163.

[113] Russo, A.; Lombardo, L.; Troncoso, N.; Garbarino, J.; Cardile, V. Rosmarinus officinalis Extract Inhibits Human Melanoma Cell Growth. *Nat. Prod. Commun.,* **2009,** *4*, 1707-1710.

[114] Johnson, J.J. Carnosol a promising anti-cancer and anti-inflammatory agent. *Cancer Lett.,* **2011,** *305*, 1–7.

[115] Huang, S.C.; Ho, C.T.; Lin-Shiau, S.Y.; Lin, J. K. Carnosol inhibits the invasion of B16/F10 mouse mela- noma cells by suppressing metalloproteinase-9 trough down-regulating nuclear factor-kappa B and c-Jun. *Biochem. Pharmacol.,* **2005,** *69*, 221–232.

[116] Tong, L.; Wu, S. The Mechanisms of Carnosol in Chemoprevention of Ultraviolet B-Light-Induced Non-Melanoma Skin Cancer Formation. *Sci. Rep.,* **2018,** *8*, 3574).

[117] Surh, Y.J. Anti-tumor promoting potential of selected spice ingredients with antioxidative and anti-inflammatory activities: a short review. *Food Chem. Toxicol.,* **2002,** *40*, 1091–1097.

[118] Surh, Y.J.; Lee, E.; Lee, J.M. Chemoprotective properties of some pungent ingredients present in red pepper and ginger. *Mutat. Res.,* **1998,** *402*, 259–267.

[119] Rehman, R.; Akram, M.; Akhtar, N.; Jabeen, Q.; Saeed, T.; Shah, S.M.A.; Ahmed, K.; Shaheen, G.; Asif, H.M. Zingiber officinale Roscoe (pharmacological activity). *J. Med. Plants Res.,* **2011,** *5*, 344-348.

[120] Kwang, K.; Kyung, S.; Jong, L.; Sang, L.; Young, S. Inhibitory effects of [6]-gingerol, a major pungent principle of ginger, on phorbol ester- induced inflammation, epidermal ornithine decarboxylase activity and skin tumor promotion in ICR mice. *Canc. let.,* **1998,** *129*, 39-144.

[121] Keum, Y.S.; Kim, J.; Lee, K.H.; Park, K.K.; Surh, Y.J.; Lee, J.M.; Lee, S.S.; Yoon, J.H.; Joo, S.Y.; Cha, I.H.; Yook, J. I. Induction of apoptosis and caspase-3 activation by chemopreventive [6]-paradol and structurally related compounds in KB cells. *Cancer Lett.,* **2002,** *177*, 41–47.

[122] Kim, E.C.; Min, J.K.; Kim, T.Y.; Lee, S.J.; Yang, H.O.; Han, S.; Kim, Y.M.; Kwon, Y.G. [6]-Gingerol, a pungent ingredient of ginger, inhibits angiogenesis in vitro and in vivo. *Biochem. Bioph. Res. Co.,* **2005,** *335*, 300–308.

[123] Davies, M.; Robinson, M.; Smith, E.; Huntley, S.; Prime, S.; Paterson, I. Induction of an Epithelial to Mesenchymal Transition in Human Immortal and Malignant Keratinocytes by TGF- b1 Involves MAPK, Smad and AP-1 Signalling Pathways. *J. Cell. Biochem.,* **2005,** *95*, 918–931.

[124] Nigam, N.; Bhui, K.; Prasad, S.; George, J.; Shukla, Y. [6]-Gingerol induces reactive oxygen species regulated mitochondrial cell death pathway in human epidermoid carcinoma A431 cells. *Chem. Biol. Interact.,* **2009,** *181*, 77–84.

[125] Cojocaru, S.I.; Stan, M.; Stoian, G.; Dinischiotu, A. Effects of Zingiber Officinale Roscoe Fresh Extract on Amelanotic Melanoma and Normal Skin Fibroblasts. *Rev. Med. Chir. Soc. Med. Nat. Iasi,* **2015,** *119*, 592-596.

[126] Fonseca, Y.M.; Catini, C.D.; Vicentini, F.T.M.C.; Nomizo, A.; Gerlach, R.F.; Fonseca, M.J.V. Protective effect of Calendula officinalis extract against UVB-induced oxidative stress in skin: Evaluation of reduced glutathione levels and matrix metalloproteinase secretion. *J. Ethnopharmacol.,* **2010,** *127,* 596–601.

[127] Ukiya, M.; Akihisa, T.; Yasukawa, K.; Tokuda, H.; Suzuki, T.; Kimura, Y. Anti-Inflammatory, Anti-Tumor-Promoting, and Cytotoxic Activities of Constituents of Marigold (Calendula officinalis) Flowers. *J. Nat. Prod.,* **2006,** *69*, 1692-1696.

[128] Sak, K.; Nguyen, T. H.; Ho, V.D.; Do, T.T.; Raal, A. Cytotoxic effect of chamomile (Matricaria recutita) and marigold (Calendula officinalis) extracts on human melanoma SK-MEL-2 and epidermoid carcinoma KB cells. *Cogent Med.,* **2017,** *4*, 1333218.

[129] Jiménez-Medina, E.; Garcia-Lora, A.; Paco, L.; Algarra, I.; Collado, A.; Garrido, F. A new extract of the plant calendula officinalis produces a dual in vitro effect: cytotoxic anti-tumor activity and lymphocyte activation. *BMC Cancer,* **2006,** *6*, 119.

[130] Preethi, K.C.; Siveen, K.S.; Kuttan, R.; Kuttan, G., Inhibition of Metastasis of B16F-10 Melanoma Cells in C57BL/6 Mice by an Extract of Calendula Officinalis L Flowers. *Asian Pac. J. Cancer Prev.* **2010,** *11,* 1773-1779.

[131] McKay, D.L.; Blumberg, J.B. A Review of the Bioactivity and Potential Health Benefits of Chamomile Tea (Matricaria recutita L.). *Phytother. Res.,* **2006,** *20*, 519–530.

[132] Matić, I.Z.; Juranić, Z.; Šavikin, K.; Zdunić, G.; Nađvinski, N.; Gođevac, D., Chamomile and Marigold Tea: Chemical Characterization and Evaluation of Anticancer Activity. *Phytother. Res.,* **2013,** *27*, 852–858.

[133] Srivastava, J.K.; Snjay, G. Antiproliferative and Apoptotic Effects of Chamomile Extract in Various Human Cancer Cells. *Agric. Food Chem.* **2007,** *55*, 9470–9478

[134] Shukla, S.; Gupta, S. Apigenin: A Promising Molecule for Cancer Prevention. *Pharm. Res.,* **2010,** *27*, 962–978.

[135] Jarrahi, M., An experimental study of the effects of Matricaria chamomilla extract on cutaneous burn wound healing in albino rats *Nat. Prod. Res.,* **2008,** *22*, 422–427.

[136] Cicerale, S.; Lucas, L.J.; Keast, R.S. Antimicrobial, antioxidant and anti-inflammatory phenolic activities in extra virgin olive oil. *Curr. Opin. Biotechnol.,* **2012,** *23*, 129-35.

[137] Serreli, G.; Deiana M. Biological Relevance of Extra Virgin Olive Oil Polyphenols Metabolites. *Antioxidants,* **2018,** *7*, 1-17.

[138] Parkinson, L.; Cicerale, S. The Health Benefiting Mechanisms of Virgin Olive Oil Phenolic Compounds. *Molecules,* **2016,** *16*, pii: E1734.

[139] Scoditti, E.; Capurso, C.; Capurso, A.; Massaro M. Vascular effects of the Mediterranean diet-part II: role of omega-3 fatty acids and olive oil polyphenols. *Vascul. Pharmacol.,* **2014** *63*, 127-34.

[140] Cicerale, S..; Conlan, X.A.; Sinclair, A.J.; Keast, R.S. Chemistry and health of olive oil phenolics. *Crit. Rev. Food Sci. Nutr.,* **2009,** *49*, 218-36.

[141] Afaq F.; Katiyar, S.K. Polyphenols: skin photoprotection and inhibition of photocarcinogenesis. *Mini Rev. Med. Chem.* **2011,** *11*, 1200-15.

[142] Polini, B.; Digiacomo, M.; Carpi, S.; Bertini, S.; Gado, F.; Saccomanni, G.; Macchia, M.; Nieri, P.; Manera, C.; Fogli, S. Oleocanthal and oleacein contribute to the in vitro therapeutic potential of extra virgin oil-derived extracts in non-melanoma skin cancer. *Toxicol. In Vitro,* **2018,** *52*, 243-250.