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Review

Advances on Natural Polyphenols as Anticancer Agents for Skin Cancer

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ABSTRACT

Polyphenols are one of most important phytochemicals distributing in herb plants, vegetables and fruits, which known as important anticancer agents. Given the high incidence and mortality of skin cancer, this study aimed to uncover the chemopreventive effects of polyphenols against skin cancer metastasis. Electronic databases including Scopus, PubMed, and Cochrane library were used to compile the literature from 2000 to August 2019. Only *in vivo* mechanistic studies with English full-texts were chosen for this review. Polyphenols were included in this study if they were administered in purified form; while total extract and fractions were excluded. Among the 8254 primarily selected papers, only a final number of 34 studies were included. The chemopreventive effects of polyphenols as anthocyanins, ellagitanins, EGCG, oleuropeindihydroxy phenyl, punicalagin, quercetin, resveratrol and theaflavin, were mainly examined in treatment of melanoma as the highly metastatic form of this cutaneous cancer. Those properties are mediated by modulation of angiogenesis, apoptosis, inflammation, metastasis, proliferation, pathways such as EGFR/MAPK, mTOR/PI3K/Akt, JAK/STAT, FAK/RTK2, PGE-2/VEGF, PGE-1/ERK/HIIF-1α, and modulation of related signals including NF-κB, $P21^{WAF/CIP1}$, Bim, Bax, Bcl2, Bclx, Bim, Puma, Noxa, ILs and MMPs. Chemopreventive effects of polyphenols are mediated by several sig-

Abbreviation: ASK1, apoptosis signal-regulating kinase 1; BCC, basal cell carcinoma; 4EBP1, 4E binding protein 1; EGCG, epigallocatechin-3-gallate; EGFR/MAPK, epidermal growth factor receptor/mitogen activated protein kinase; FAK, focal Adhesion Kinase; FOXO1, forehead box O1; GM-CSF, granulocyte-macrophage colony-stimulating factor; G-CSF, granulocyte-colonystimulating factor; GTPs, green tea polyphenols; HIF1α, hypoxia inducible factor 1-α; HUVECs, Human umbilical vein endothelial cells; IL-6Rα, IL-6 signal transducing receptor; mPGEs, microsomal prostaglandin-E synthase-1; MMP, Matrix Metalloproteinase; mTOR, Mammalian Target Of Rapamycin; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NMSC, Non-melanoma skin cancer; PCNA, proliferating cell nuclear antigen; PI3K/Akt, phosphatidylinositide 3-kinases/protein kinase B; SCC, squamous cell carcinoma; SOCS3, suppressor of cytokine signaling; STAT3, Signal transducer and activator of transcription; PTK2, Protein tyrosine kinase 2; TIMP2, Tissue inhibitor of metalloproteinase 2; VCAM, Vascular cell adhesion molecule

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naling pathways against skin carcinogenesis and metastasis, implying the importance of polyphenols to open up new horizons in development of anti-skin cancer therapeutic strategies.

1. Introduction

Skin cancer is a result of several mutations in cancer-related genes including proto-oncogenes and tumor suppressors in skin cells, which causes an imbalance in cell homeostasis and excessive cutaneous cell proliferation [1]. According to the epidemiologic studies, skin cancer is considered as the most prevalent type of cancer worldwide with a positive growth rate of prevalence and mortality in comparison to other diseases [2]. Furthermore, according to U.S statistics, the average of total cost spent for skin cancer treatment annually is doubled within 5 years [3]. Therefore, morbidity will remain as the unfavorable consequence of skin cancer development and continue to put an economic burden on world health system.

Based on the cell type, cutaneous melanoma and non-melanoma are the main classes of skin cancer. Non-melanoma skin cancer (NMSC) is originated from keratinocytes of epidermis and is divided in two main subdivisions which are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Although BCC is the most prevalent form of skin cancer, it has the lowest mortality rate because of its low potential to metastasize. In contrast to BCC, melanoma, originating from melanocytes at the deepest layer of epidermis, has the lowest prevalence rate (4%), but the worst prognosis, and is responsible for the 80% of mortality cases from skin cancer [4]. Skin cancer survival rate is high and it is curable if diagnosed in early stages; however, the metastatic form has a poor prognosis. Melanoma progression is required for the multistep changes of melanocyte characteristics. The first step is to gain ability to proliferate and survive which help to grow horizontally to develop the melanoma tumor. In the next step, the melanoma cells should be able to grow vertically and invade to the deep layers of dermis. This enables melanoma cells to reach endothelium layer and start distant metastasis via blood circulation [5]. These traits mostly acquired by key triggers including BRAF and NRAS mutations; however, these mutations alone could not cause metastatic form of melanoma. For example, mutations of oncogenes like V600E BRAF are activated in melanocyte nevi (moles), but they do not cause development of malignancy [6]. Apart from melanocyte mutations' effect on melanomagenesis, micro-environmental factors including extracellular matrix, microvasculature, growth factors and cytokines are important during this process [7].

Current treatments for the management of metastatic and/or non-metastatic melanoma include chemotherapy, immunotherapy, radiotherapy and targeted therapy which are expensive, highly toxic and, in some cases, ineffective due to resistance especially in metastatic form [8]. So, it is important to investigate new effective therapeutic strategies which are also affordable.

Medicinal plants have a long history in disease treatments which arise from their availability and affordability. From the 174 anticancer drugs in the market, between 1981 and 2014, only 23 were totally synthetic and 5 vaccines. All the others, 146, were correlated to natural products as biological, natural products unmodified in structure, though might be semi- or totally synthetic, "botanical drug" (in general these have been recently approved), derived from a natural product and usually with a semisynthetic modification. The last group, even made by total synthesis, has a pharmacophore that is/was from a natural product. For instance, combretastatins are a class of natural phenols highly methylated and with a similarity of different natural polyphenols. Thus should be considering for further research in cancer therapy.

Numerous phytochemicals gained lots of attention for numerous diseases even in chemoprevention and for cancer adjuvant treatment in last decades [9,10]. Thus, once among them polyphenols, that are well

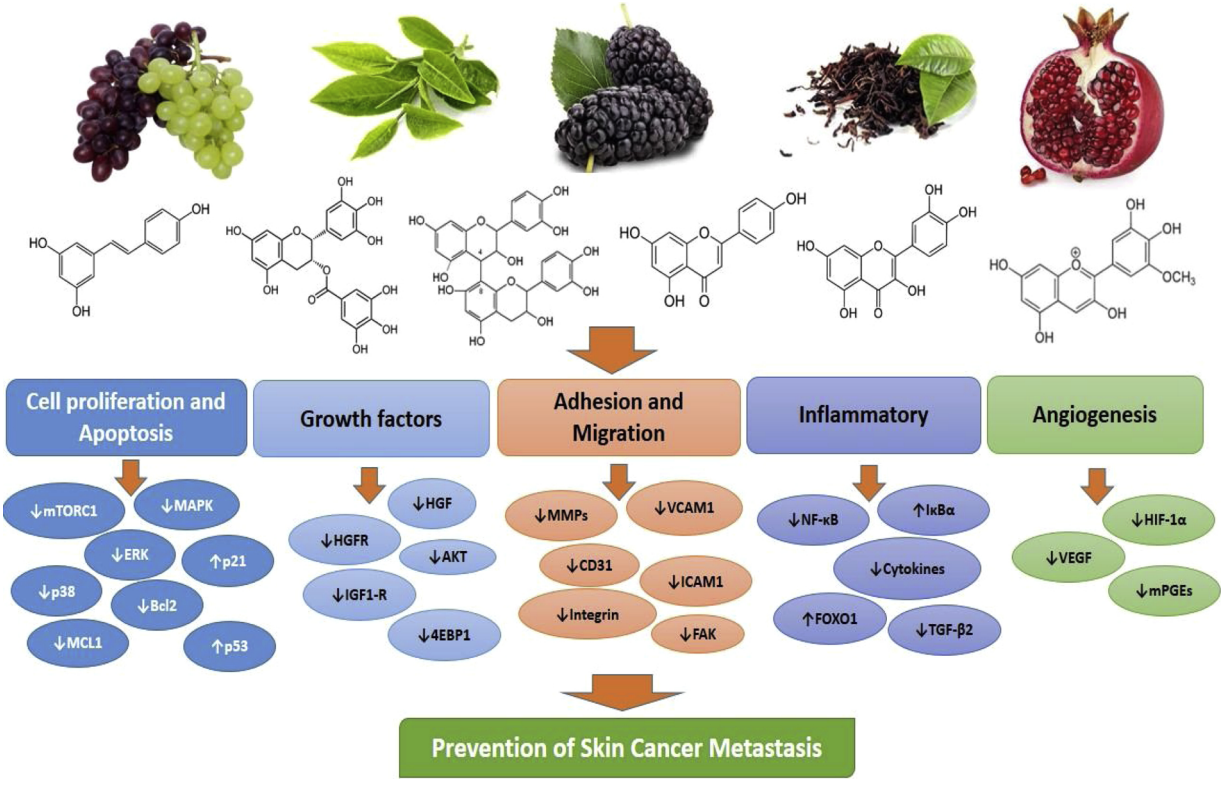

Fig. 1. The preventive effects of several polyphenols from herbs mediated by a number of signaling factors.

tolerated, and have various bio-effects correlated to this pathology, as will be explained below. They will be suitable potential candidates, for instance, to control metastasis of malignant cells [11].

Bioavailability of polyphenols is defined as the extent of substance which reached to the circular system and distributed in several tissues [12]. Not surprisingly, bioavailability and biotransformation seems to be the two causal hallmarks which influence on effectiveness of polyphenols. On the basis of dimension, polyphenols may weakly and/or without hindrances absorb to the gut interfaces. What is more, it has been suggested that polyphenols are commonly found as conjugated forms in the plasma. However, conjugation with proteins in oral cavity and acidic pH of stomach has been shown to not change the stability and biological activity of polyphenols [13–15]. Enzymatic glucuronidation and methylation of polyphenols in small intestine may affect the absorbance of polyphenolic reagents [16,17]. After absorbance, they modified by several additional groups such methyl, glucuronide, and sulfate ester in several tissues inside the body. Albeit in skin, convenient penetration of herbal polyphenols needs to be formulated with hydrophobic-, organic- and cream-based compounds because of hydrophobic characteristics of outer layer of dermal tissues [18]. In light of the low bioavailability, nano-, macro- derivation, and co-administration and bioengineering-based approaches were developed to enhance the bioavailability, biological activity and effectiveness of polyphenols. The biological activity of polyphenols was considerably affected by metabolic transformation leading to the possible diversities and controversies in the results of associated studies. For instance, *Cis* and *Trans* isoforms of resveratrol highly affect its variable efficacy and bioactivity [19,20]. Polyphenolic compounds have been shown to be transformed via several enzymes in liver, small intestine and colon. As mentioned above, almost number of polyphenols is found to be absorbed through digestive system and conjugated with several additional groups including glycosides. Unabsorbed polyphenols are indicated that transformed and used by colonic microbiota [21]. This biotransformation of polyphenols through flora microbiota is required to absorption of these compounds in intestine. For example, biotransformation of some non-absorbed catechins from green tea using intestinal bacteria converted them to easily absorbed simple polyphenolics [22]. From above, it could be concluded that biotransformation of polyphenols through several enzymes and also gut microbiota affect their availability and biological activity.

In this review, based on the latest research, phytochemicals with potential to inhibit metastasis of melanoma and their mechanisms of actions are discussed based on the most recent studies (Fig. 1).

2. Study design

Electronic databases including PubMed, Cochrane library and Scopus were searched using the keywords ("Skin cancer" OR "skin neoplasm" OR "skin malignancy" OR "basal cell carcinoma" OR "squamous cell carcinoma" OR "melanoma") [title/abstract/keyword] AND ("plant" OR "extract" OR "herb" OR "phytochemical" OR "polyphenol" OR "flavonoid" OR "lignin" OR "coumarin" OR "curcumin" OR "resveratrol") [all fields]. Datasets were outlined from 2000 to August 2019 which was updated in June 2018 in order to add latest published papers. To find relevant studies, articles were primarily screened based on titles and abstracts by two independent researchers. To confine the search, only English language papers were included in this review. Inclusion criteria were herbal polyphenols assessed in the purified form *in vivo* in all types of skin cancer which focused on the metastasis-related mechanisms. Exclusion criteria were papers evaluating the effect of total extracts or fractions instead of purified compounds, synthetic compounds, non-herbal materials, lack of mechanistic evaluation of metastasis and lack of *in vivo* assessments. The flow diagram of the studies selection process is presented in Fig. 2.

3. Polyphenols as anti-skin cancer agents

Cancer preventive and therapeutic potential of natural agents such as polyphenols have been demonstrated in several preclinical, clinical and epidemiologic studies. Polyphenols with at least one aromatic ring

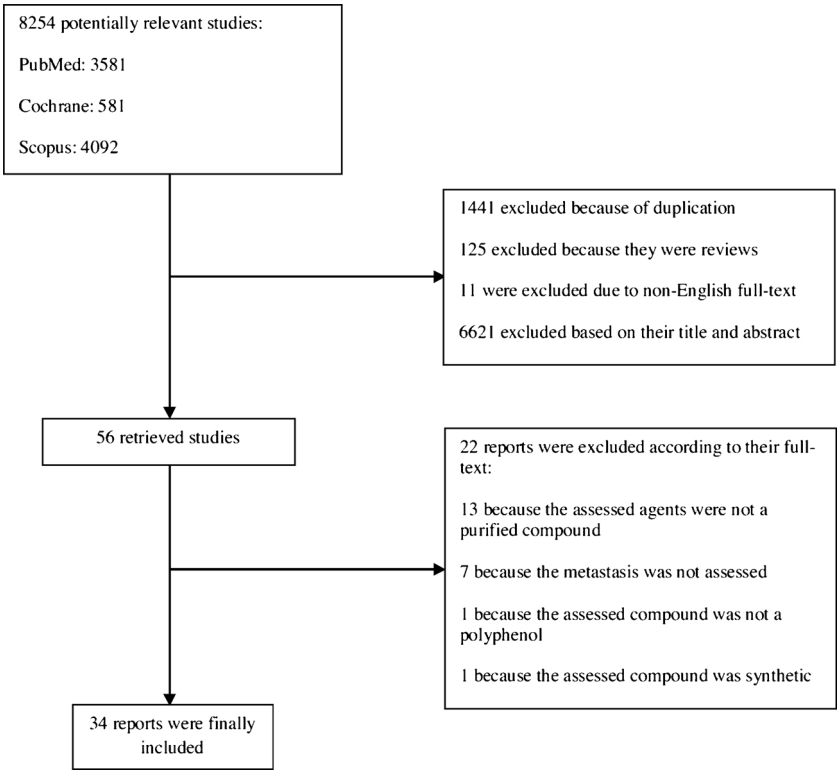

Fig. 2. Flow diagram related to selection process of papers.

and hydroxyl group encompass a wide spectrum of secondary metabolites [23]. Accumulating evidence from the last decades reveals the promising anticancer efficiency of some of these compounds such as anthocyanins, epigallocatechin-3-gallate (EGCG), resveratrol, among others isolated from plants [24–28]. Polyphenols are the most abundant natural antioxidants in human diet. Rich source of these phytochemicals are fruit, vegetables, cereals, chocolate, olive oil, and beverages namely tea and wine.

Resveratrol, as a phytoalexin derived from more than 70 plant sources including grapes, pines, plums, berries and peanuts, which is produced and secreted in response to environmental stimulators such as stress and pathogens [29]. In preclinical studies, the anticancer effects of resveratrol have been examined in skin, breast, prostate, gastrointestinal and lung cancers [30]. The underlying antigrowth mechanisms of resveratrol in mouse skin carcinogenesis models have been shown to be due to induction of antioxidant systems, apoptosis, amelioration of inflammation and cell cycle suppression [31–35]. In the 7, 12- dimethylbenz(a)anthracene (DMBA) induced mammary tumors and xenograft breast cancer animal models, resveratrol showed growth inhibitory effects through the down regulation of proliferation and angiogenesis, induction of apoptosis, as well as the modulation of hormones such as estrogen, progesterone and their receptors [36–40]. Modulation of genetics and epigenetic factors has been suggested as the principal anticancer mechanisms of resveratrol. In this line, resveratrol inhibits the activity of DNA methyltransferases through demethylation of tumor suppressive genes in esophageal, gastric and colorectal cancer cells [41]. The cancer modulating effects of resveratrol was also demonstrated in a few clinical studies. The phase I study showed the antigrowth effects of resveratrol in lymphoma and colon cancers. Albeit, clinical studies of resveratrol should be continued to develop a drug with full chemopreventive and therapeutic potentials [30].

EGCG, its synthetic analogs and prodrugs are widely studied polyphenols in cancer prevention and treatment. Various studies documented its antitumor properties [42–47). Curcumin, a polyphenol extracted from the *Curcuma longa* L., show several biological activities such as antioxidant, anti-inflammatory and anticancer effects [48,49]. The chemopreventive effects of this compound have been demonstrated in several tumors mediated by induction of apoptosis [49,50]. In a recent study, the anti-metastatic effects of chitosan-coated-nanoparticles containing curcumin was reported *in vitro* and *in vivo* by suppression of cell viability and induction of apoptosis [51].

Those are some of the more identified examples, however these model structures can be amplify for further research with similarities with them.

4. Signaling pathways involved in preventive effects of polyphenols against skin cancer metastasis

Whereas several biological processes had been targeted for cancer treatment, cellular processes such as gene expression, cell cycle progression, development of proliferation and migration are considered key factors in cancer regulation and prevention. The anticancer and the cytoprotective properties of polyphenols are generally attributed to their antioxidant and pro-oxidant properties [52]. With respect to pro-oxidant activity, polyphenols are able to generate ROS in cancer cells that lead to induction of apoptosis, suppression of cell cycle and down-regulation of proliferation through modulation of several signaling pathways such as epidermal growth factor receptor/mitogen activated protein kinase (EGFR/MAPK), phosphatidylinositide 3-kinases/protein kinase B (PI3K/Akt) [53,54], and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) [55] and [4] anti-inflammatory factors [56].

Different polyphenols exhibit anticancer properties through their own unique targeting systems. Some of the commonly known pathways are discussed below (Fig. 3).

5. Cell proliferation and apoptosis

Cell proliferation can be defined as the cyclic behavior of the cells (*i.e* how quickly cells pass through the four phases of G_1, S, G_2 and M)

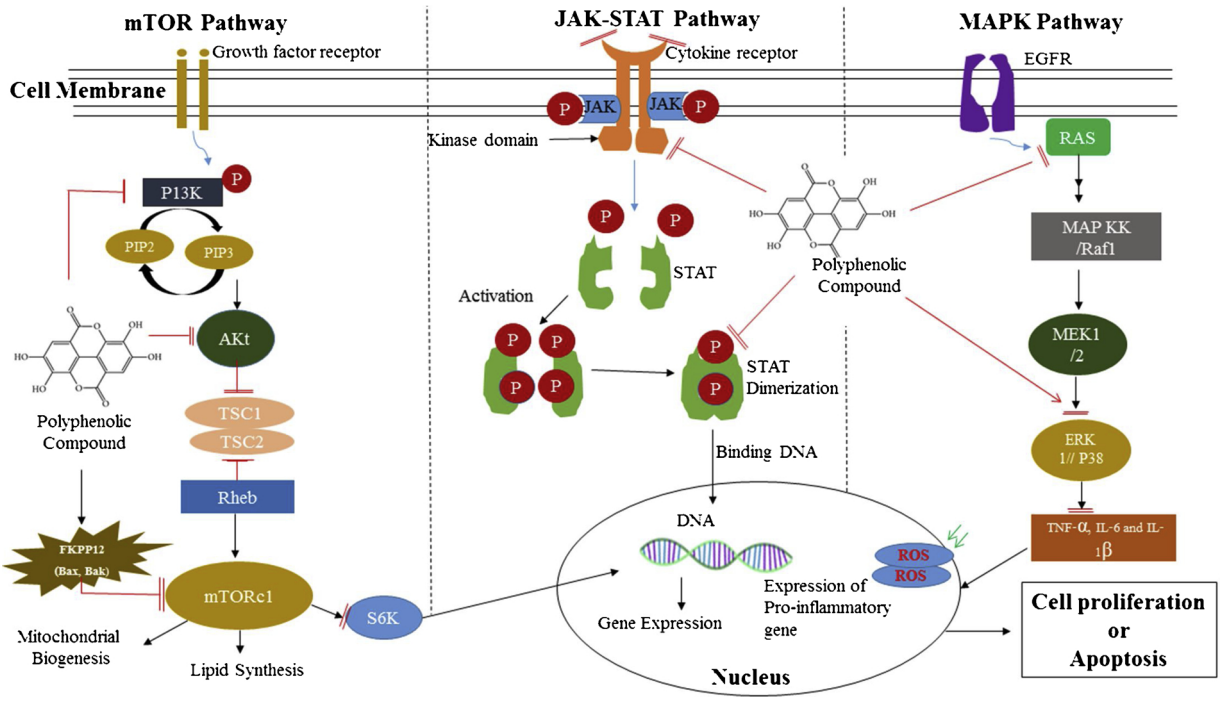

Fig. 3. [1] Control of tumor progression through check points by polyphenols in mTOR signalling pathways (i) reducing the expression of PI3K (ii) Hypo-phosphorylation of pRb, induce the expression of pro-apoptotic Bax, Bak, blocking phosphorylation of S6K1 and AKT Ser473 residue. [2] Inhibition of JAK-STAT pathway by polyphenol (i) suppressing the activation signaling molecules (IL's and GF's) (ii) Inhibit MMP-2 (iii) suppressed phosphorylation of HER-2 and Cdk's [3], MAPK is regulated through (i) UVB-induced phosphorylation of ERK1/2, JNK and p38 proteins (ii) activation of intracellular ROS, (iii) Inhibit level of TNF-α, IL-6 and IL-1β.

and the number of cells that are active cycling in a cell cycle. Apoptosis is the controlled and/or programed cell death occurring at a continuous phase. It is a process by which dysregulated cells in the body are removed and the balance is maintained between the generation of fresh and removal of the old ones; thereby maintaining the accurate number of cells in a tissue. Several polyphenols are known to control cancerous cell growth through inhibition of cell proliferation and induction of apoptosis mainly regulated through mTOR/PI3K/AKT, STAT3, MAPK/ERK, Ras-Raf and JNK p38 signaling pathways and cell arrest in different stages of cell cycle (Fig. 1).

5.1. Mammalian Target of Rapamycin (mTOR)

Phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) is a chain of signalling pathway as the members of serine/threonine protein kinase family which are responsible for physiological processes such as proliferation, motility, survival and growth of cells, gene transcription, protein synthesis and autophagy. mTOR is regulated through several activation points and phosphorylation of effector kinases and is one of the targets of polyphenols in inhibition of cancerous cells growth.

Green tea polyphenols (GTPs) are the most studied natural polyphenols for their antioxidant properties. It has been reported that protease inhibitor MG132 in combination with GTPs in cells resulted to apoptosis through degradation of class I HDACs (Histone deacetylase) and induction of cell cycle arrest in the G_0/G_1 phase [57]. GTPs lead to increased accessibility of histone H3 with the promoter region of the $p21^{WAF1/CIP1}$ and Bax gene in cancer cells through proteosomal degradation of class I HDACs and enhanced acetylation of histone H3.

EGCG, an important polyphenol from GTPs, is known to inhibit and prevent cancer by extending the cell viability through induced autophagy in mTOR-dependent and PKA-independent pathways. EGCG delays apoptotic cell death by up-regulating autophagy-dependent survival, thus forming a major asset in control of cancerous cell proliferation and survival [58]. The anti-proliferative effects of EGCG in skin cancer was attributed to the retinoblastoma (pRb) ± E2F/DP pathway by Ahmad et al.(2002) [59].Treatment of cells with EGCG resulted in down regulation of pRb and other members of the pRb family. Hypophosphorylation of pRb also leads to recruitment of free E2F and subsequently suppression of cell cycle progression at G0/G1 phase transition and apoptotic cell death [59]. Singh and Katiyar found that EGCG is able to down-regulate the expression of cAMP in skin cancer cells by reducing the expression of PI3K and p-Akt proteins. In addition, exposure of cells to EGCG is associated with reduction the expression of c-Myc and VEGF, as the downstream targets of β-catenin [56].

Rapamycin, is an important inhibitor of mTOR pathway which inhibits the kinase activity of mTORC1 by binding to prolyl isomerase (PPIase) and, is also, an activator of mTORC1, RHEB. The inhibition of TPA-induced mTORC1 and AKT (Thr308, Ser473) by rapamycin results in a significant reduction of the number of labeled epidermal cells, induction of hyperplasia and mTORC2 upon prolong exposure. These processes were associated with dramatic decrease of inflamed cutaneous cells and reduced infiltration T cells, macrophages, neutrophils, NK cells and mast inflammatory cells [60]. Loss of RICTOR/mTORC2 may also lead to dephosphorylation of AKT at Ser473 and forehead box O1 and O3 (FOXO1 and FOXO3) transcription factors [61]. Changes in the mTOR pathway by down regulating the PTEN and TSC2 effector are moreover reported from rapamycin against tumour cells [62].

Phenolic and polyphenic compounds, like anthocyanins from pomegranate, proanthocyanidins from grapes and caffeic acid found in many natural sources, show an important potential in the inhibition of mTORC1 activities by blocking the phosphorylation of S6K1 and AKT at Ser473 residue mediating by mTORC1. Other mechanisms may include, mTOR kinase inhibitor as well as, ATP competitive inhibitors of mTOR, DNA-PK, and PI3K [52,63–68].

Resveratrol is another polyphenol known to induce the suppression of cell cycle at S phase through ATM/ATR-Chk1/2-Cdc25C pathway by phosphorylation of Cdc2-tyr15 [69]. ATM phosphorylates and stabilize p53 which followed by p53-dependent G1/S cell cycle arrest. It has been shown that resveratrol lead to cell cycle arrest at the S and G2/M phases through inhibition of Cdk7 and p34 Cdc2 kinases. Additionally, resveratrol supresses the proliferation of human epidermal carcinoma cells through decreasing of the expression of cyclin D1, cyclin D2, and cyclin E) resulting in down regulation of cdk-2, cdk-4 and cdk-6) and upregulation of p21WAF1/CIP1 [69–71]. Resveratrol is also known to increase the expression of pro-apoptotic Bax, Bak, PUMA, Noxa, and Bim, and decreases the expression of anti-apoptotic Bcl2, Bcl-XL, and Mcl-1 by modulation of the mitochondrial death pathway [69].

5.2. Signal transducer and activator of transcription (STAT3)

STAT3 is a transcription protein, mediating the expression of a variety of genes in response to cell stimuli, and is also a potential target for inhibition of cell proliferation and apoptosis which are mostly activated by cytokines (IL-6, IL-17 and IL-22) and growth factors (EGF & FGF) [72]. Polyphenols have the ability to inhibit the expression of STAT3 either by blocking the activity of JAK or suppressing the activation of signaling molecules (IL's and GF's). Apigenin and luteolin, are able to inhibit IL-6 and modulate the expression of IL-6 signal transducing receptor (IL-6Rα) and suppressor of cytokine signaling (SOCS3) protein. The inhibitory effect on the expression and secretion of the extracellular matrix degrading enzyme, matrix metalloproteinase-2 (MMP-2), has been credited to regulate the STAT3 pathways [73]. Myricetin and resveratrol are known to directly bind to the catalytic domain of the JAK1 protein and inhibit the phosphorylation of STAT3/JAK1 [74,75]. Quercetin is reported to suppress the activation of STAT3 by IL-6 through reduction of cyclin D1 and the secretion of MMP-2. It results in inhibition of cell proliferation and migration through accumulation of cells in S and G2/M proliferative phases of the cell cycle [76,77]. The role of EGCG in suppression of STAT3 activation is achieved by suppressed phosphorylation of HER-2 that further correlates with suppressing the promoter of c-fos and cyclin D1 and enhancement the levels of cyclin D1 and Bcl-XL leading to cell cycle arrest and apoptosis [78].

Butein, a polyphenol extracted from *Butea frondosa*, was reported to suppress the IL-6-inducible and constitutive forms of STAT3 through inhibition of tyrosine kinases as JAK1, JAK2 and c-Src signaling proteins. In addition, this compound down-regulated the expression of STAT3 target genes like Bcl-xL, Bcl-2, cyclin D1, and Mcl-1 causing an elevated stage of apoptosis [79]. In the case of the compounds celastrol and curcumin, they inhibit the constitutive and IL-6-induced activation of STAT3 and phosphorylated STAT3, leading to a decrease in the mRNA expression level of Bcl-2 and increase in the accumulation of cells in the sub-G1 and G2/M phase, respectively. It further results in activation of caspase-3, ensuing a suppressed cell proliferation and induced apoptosis [77,80].

The MAPK/ERK pathway, also known as Ras-Raf cascade, is a group of serine/threonine proteins including the c-Jun NH2-terminal kinases (JNK), and p38 that communicates signals from a receptor protein on the surface of the cell to the DNA in the nucleus of the cell. Overexpression and/or mutation in the signaling factors are the common hallmark of proliferative disorders such as cancer is involved in tumor initiation, progression and metastasis. Several polyphenols have been recognized to regulates the MAPK/ERK pathway and thus inhibit the cancerous cell growth. Among the prominent ones, silymarin, retinoids, and GTPs like EGCG are known to effectively reduce UVB-induced phosphorylation of ERK1/2, JNK and p38 proteins of the MAPK family. GTPs are able to inhibit UVB-induced translocation of NF-κB/p65 and NF-κB/p65 DNA-binding activity followed by activation of IKKα, phosphorylation and degradation of IαBα [81]. In the specific case of EGCG, it also controls cell proliferation in tumor cells by inhibiting phosphorylation of ERK1/2, JNK, p38 proteins and H_2O_2 generation, leading to inactivation and suppression of MAPK pathways

[63,82]. Inactivation of MAPK pathways and other cell proliferative routes was also achieved by peritoneal mast cells incubated with GTPs through reduced production of histamine. The underlying mechanism of histamine depletion is mediated by a garlic acid-mediated raise in the level of cAMP and reduction in the content of intracellular calcium which ultimately leads to inhibition of pro-inflammatory cytokines, TNF-α and IL-6 through inactivation of NF-κB and p38 MAPK signaling factors [83].

Similar anti-apoptotic properties of polyphenols from black tea (theaflavins and thearubigins) were reported by Bhattacharya et al. [108] via induction of cell death in tumor cells through activation of intracellular ROS generation. They induce apoptotic death of human malignant melanoma cells (A375) through activation of apoptosis signal-regulating kinase 1 (ASK1), MAPK kinase, and JNK–p38 cascade.

Proanthocyanidins extracted from grape seeds, as well as anthocyanins and ellagitannins from pomegranate fruit were found to have dose- and time-dependent inhibition of irradiation-induced phosphorylation of ERK1/2, JNK1/2, p38 and Akt signalling factors by reactivation of MAPK phosphatases and induction of MAPKs cascades [84]. The inhibition of TNF-□, IL-6 and IL-1□□content in skin tumour cells was reported [67,85].

6. Growth factors

Growth factors are glycoproteins secreted by the cells of the immune, fibroblast, and endothelium and epithelium system. They play vital role in proliferation, motility, and invasion of cancerous cells. Growth factors employ or activate different c-jun proto-oncogenes and downstream signals through various signaling pathways such as Lyn/JAK/STAT3 or MAPK/ERK1/2 pathways leading to cell proliferation and invasion [86]. Although numerous growth factors are present in human body, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), insulin-like growth factor-1 receptor, and the vascular endothelial growth factor (VEGF) are the more prominent ones in the development of non-melanoma skin cancers (Fig. 4) [87].

The concentration of HGF, VEGF, IGF-I and IGFBP-3 in serum was observed to be significantly reduced in patients treated with EGCG by inhibiting the phosphorylation of ERK p42/p44 [88]. This compound is able to inhibit HGF-induced migration and invasion of parental and HGF/SF-transfected B16F10 melanoma cells via blocking the Inl B-dependent activation of Met and blocking activation of Met receptor which is upstream of ERK1/2 and p70S6 kinase as reported [69]. EGCG under hypoxic conditions secretes a soluble VEGF receptor that inactivates VEGF and thus exerts anti-angiogenic effects [89]. In the case of curcumin, the treatment of keratinocyte cells with this compound could inhibit IGF-1-induced phosphorylation of the IGF-1 receptor, insulin receptor substrate-1, Akt, S6K, and 4EBP1 in a dose-dependent manner. It also lowered the TPA-induced phosphorylation of Akt, S6 kinase (S6K), and eukaryotic translation initiation factor 4E binding protein 1 (4EBP1) [90].

For resveratrol, the results of the research published show that is able to inhibit the proliferation and induce the apoptosis in human multiple myeloma (MM) cells by interference with the signalling pathways initiated by IL-1b [70].

The anti-angiogenic effects of rapamycin in inhibition of hypoxia-induced and VEGF-induced endothelial cell proliferation were reported by Guba et al. [81]. Rapamycin also decreased the production of VEGF by cancer cells through the inhibition of mTORC1-dependent translation and activity of HIF1α [91–93]. Resveratrol has been shown to mediate disruptions of Src kinase activation mediated by ROS and VE-cadherin tyrosine phosphorylation showing the critical impact on the inhibition of VEGF-induced angiogenesis [94].

7. Adhesion and Migration

Cell adhesion to the extracellular matrix (ECM) is a key factor for regulation of cellular morphology, migration, proliferation, survival, and differentiation. MMPs, focal Adhesion Kinase (FAK), vascular cell adhesion molecule (VCAM), and E-cadherin are important regulators for cell adhesion and migration and thereby, are the targets of cancer research (Fig. 4).

MMPs are a class of zinc-containing endopeptidases with a specific substrate known to involve in various pathophysiological processes including aging, healing of cutaneous wound, and angiogenesis. MMPs are activated through several processes like MAPK and NF-κB upon

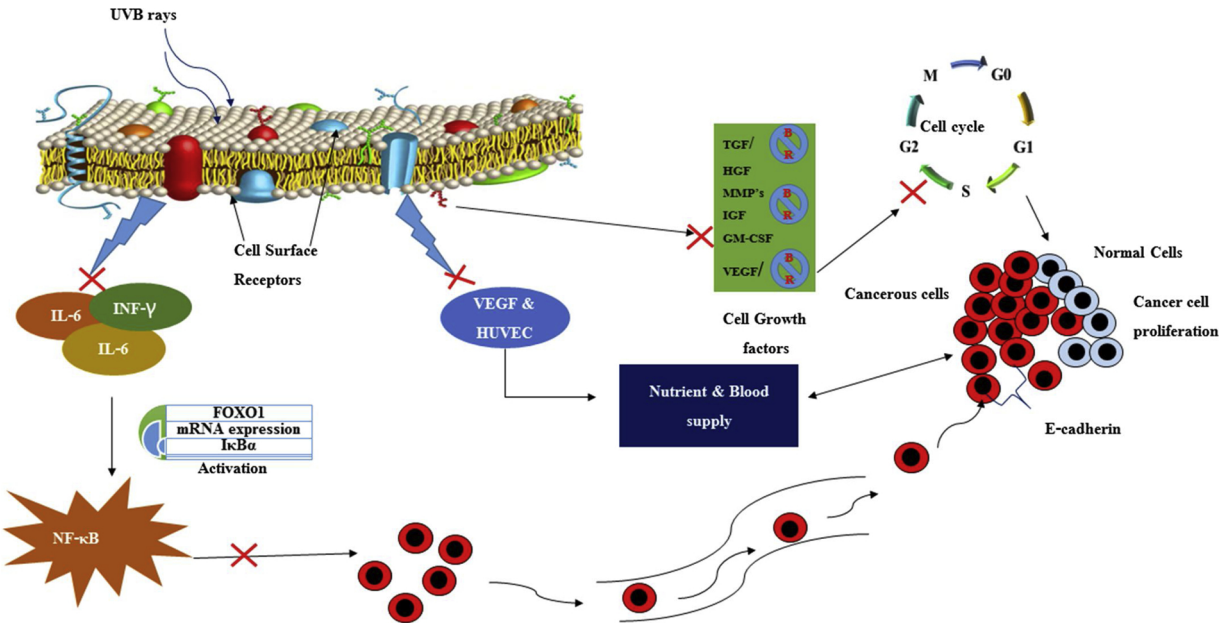

Fig. 4. Polyphenols reducing the activity GF (Growth factors) through (i) blocking activation of upstream ERK1/2 and p70S6 kinase (ii) secretes binding receptors for VEGF (iii) Lowered the TPA-induced phosphorylation of Akt & S6 kinase (S6K). Adhesion and Migration is regulated by (i) inhibiting the expression of MMP's (ii) Recovery of UVB induced procollagen type I (iii) Modulates LPS-induced expressions of ICAM-1 and VCAM-1 (iv) Upregulation of forkhead box O1 (FOXO1) and IκBα to suppress activity of NF-κB.

exposure to UVB radiations (290-320 nm), causing degradation of collagen and elastin, reduction in procollagen synthesis and subsequently, photoaging of cells [95]. It has been suggested that inhibition of UVB irradiation leads to reduced expressions of collagenase (MMP-1), gelatinase (MMP-2, MMP-9), stromelysin (MMP-3), marilysin (MMP-7), and elastase (MMP-12) subsequent reduction of NF-κB activation, down regulation of proapoptotic caspase-3, and of the cell cycle arrest in G0/G1 phase resulting in angiogenesis and formation of tumour mass [96,97].

Several polyphenol members of the Rubiaceae family exhibit anti-photoaging activity via inhibiting the expression of MMP-1, MMP-3, and MMP-9, and of MAPK [98,99]. GTPs added in drinking water to mice were recognized to reduce UVB-mediated increase in MMP-2 and MMP-9, CD31, VEGF, and proliferating cell nuclear antigen (PCNA) resulting in increased production of cytotoxic $CD8^+$ T cells and greater activation of caspase-3 as well as inhibition of AP-1 activity in the tumour cells [81].

Resveratrol by reducing the level of MMP-2 and MMP-9 was reported to inhibit the invasion of a number of cancer cells such as oral, human bladder, lung adenocarcinoma, breast, skin and so on. In addition, DMBA-induced MMP-9 expression was inhibited by resveratrol through suppression of NF-κB DNA-binding activity and activation of AP-1 signalling factor [100]. EGCG was found to competitively inhibit the phosphorylation of ELK-1 by ERK1/2 through competing to bind the active site on ERK1/2, JNK and p38 [101]. Other potential inhibitory routes of MMPs in cancer include inhibition of TGF-β [102], ameliorated RNA levels of MMPs, procollagen type I, TNF-α, and IL-6 by rosmarinic and caffeic acid [103].

Pomegranate extracts containing ellagitannins and anthocyanins significantly increases the expression of miR-126 in VCAM-1 that regulates and controls VCAM expression in response to cytokines. They are responsible for down-regulation of pro-inflammatory enzymes NOS and COX-2 messenger RNA (mRNA) and their protein expression in epithelial cells. Besides, ellagitannins and anthocyanins suppress NF-κB and inhibit phosphorylation of PI3K/AKT, as well as mTOR expression [100]. Theaflavins, from black tea, inhibit the level of adhesion molecules through inhibition of NF-κB and JNK activation in intestinal epithelial cells. These compounds also down-regulate the LPS-induced expressions of ICAM-1 and VCAM-1 through JNK signaling pathway [104]. The suppression of Akt, NOSs and PVQ-induced PDT effects causes significant apoptosis in VCAM-1(+) and HUVECs by inducing self-destruction of cells through ROS generation and are therefore considered to be beneficial against melanoma cell adhesion [105,106].

Focal adhesion kinase (FAK)/ Protein tyrosine kinase 2 (PTK2) as a cytoplasmic protein tyrosine kinase is responsible for cell adhesion, chromatin condensation and nuclear fragmentation during apoptosis. Overexpression of FAK is associated with inhibition of apoptosis and an increase in the prevalence of metastatic tumors or advanced-stage solid cancers [107]. Cellular motility, survival and proliferation via FAK is mediated by kinase-dependent and kinase-independent mechanisms. FAK are mostly regulated by NF-κB and p53 signaling pathways.

Dieckol, a polyphenol from *Ecklonia cava*, suppressed the migration and invasion of HT1080 human fibrosarcoma cells by phosphorylation and inhibition the expression of FAK [108]. Polyphenol-enriched extracts from *Hibiscus sabdariffa* were found to regulate the metastasis of cancer cells through increased tissue inhibitor of metalloproteinases 2 (TIMP2) and suppression of FAK and CD44/c-MET signaling [109]. Anthocyanins from this plant were also reported to inhibit migration of B16-F1 cells negative modulation of HUVECs tube formation through inhibition of the PI3K/Akt and Ras/MAPK cascade pathways and its downstream effectors VEGF and MMP-2/-9 [110]. Similarly, a mulberry polyphenol extract show to be capable to inhibit FAK/Src/PI3K signaling pathway and related factors like FAK, Src, PI3K, Akt, c-Raf interaction. It showed that MPE reduced the expression of small GTPases (RhoA, Cdc42 and Rac1) to affect F-actin cytoskeleton rearrangement, down regulated expression of MMP2 and vascular endothelial growth factor (VEGF) mRNA through NFκB signaling and thereby inhibited A7r5 cell migration [72].

E-cadherin is a cell-cell binding protein Ca^{2+}-dependent manner and found in epithelial tissue. Loss of E-cadherin expression is a hall mark associated with late tumor stage [65]. Polyphenols extracted from olive oil, as oleuropein, hydroxytyrosol, and verbascoside were able to attenuate the TGFβ1/Smad pathway in Met5A. Treatment with olive oil extracts along with TGFβ1 leads to an increase in the expression of E-cadherin and its promoter activity in mesothelial cells, Met5A; while phosphorylating SMAD3 and reducing transactivation of SMAD4 in MeT5A cells. Displacement of SNAIL, from nuclear compartment, was also observed [111]. Black tea extracts were reported to induce upregulation of E-cadherin as an epithelial marker as well as SNAIL-1 and Vimentin as mesenchymal markers. BET is also shown to have anti-EMT properties through inhibiting the phosphorylated forms of FAK and paxillin in carcinoma cells [112]. Drugs like tamoxifen are popular for blocking the activation of the transforming growth factor (TGF)-β1 and subsequently, the mesothelial-to-mesenchymal transition (MMT) through reduction of E-cadherin and mesenchymal-associated molecules such as SNAIL, fibronectin, collagen-I, α-smooth muscle actin, and MMP-2 [113].

8. Inflammation (TNF-α, ILs, IFNγ, NF-κB)

TNF-α is an important inflammatory cytokine involved in inflammatory signaling pathways. Upon activation by macrophages or other cells of the immune system, conformational change occurred to dissociate TNF-α from the intracellular death domain. This leads to association of the adaptor protein TRADD to the death domain, causing the modulation of the NF-κB and MAPK pathways, and death signaling through cysteine protease caspase-8.

Polyphenols from different natural sources have been successfully used for inhibition of TNF-α. For instance, punicalagin from pomegranate was used to protect human dermal fibroblasts against cell death induced by UV irradiation through down regulation of - NF-κB caspase-3, and upregulation of G0/G1 phase transition and DNA repair mechanisms [66]. Other polyphenol compounds, such as EGCG and resveratrol, could effectively alleviate UVB-induced ROS upregulation of IL-6 and TNF-α, mRNA levels and then reduced the expression of NF-κB, resulting in overall anti-inflammatory activity [114]. Resveratrol reduce the expression of transforming growth factor-β2 (TGF-β2) induced by UVB exposure in skin cells which is associated with blockade of TGF-β2/Smad-dependent and -independent pathways [90]. While most polyphenols target TNF factors, grape polyphenols upregulate forkhead box O1 (FOXO1) and IκBα, thus inhibiting NF-κB activity [115]. In the case of the structures of theaflavins, from black tea prevent inflammation by inhibition of integrin linked kinases (ILK) and NF-κB signaling pathways and suppression of TNF-α [116,117].

Comparative evaluation among GTPs and BTP in suppression of adverse effect of TNF-α induced inflammation showed that both extracts were highly potent in inhibiting TNF-α by reversing the down regulation of TNF-α through increase in alkaline phosphatase concentration [118]. Other example, includes the study involving Kuding tea polyphenols (HKTP) that were able to reduced serum levels of IL-6, IL-12, TNF-α, IL-1β, interferon-γ (IFN-γ), motilin (MOT), IL-6 mRNA expression by lowering the expression of MAPK, NF-κB, inducible NOS (iNOS), and cyclooxygenase-2 (COX-2) [119]. In a recent work, Callcott et al. [111] showed that colored rice-derived polyphenols might interact with biochemical pathways to elicit their antioxidant and anti-inflammatory activity. In particular, the suppression of TNF-α by colored rice polyphenols extract through a reduce malondialdehyde without modulating plasma IL-6 concentrations was reported [120]. The extract is principally comprised of anthocyanins being cyanidin-3-glucoside and peonidin-3-glucoside the most abundant.

As understood that TNF-α phosphorylates Akt in a PI3K- and NF-kB-dependent way blocking the phosphatidylinositol 3-kinase (PI3K), and

Table 1
cancer preventive effect of polyphenols in skin cancer models and their molecular mechanisms.

1-Name	*In vivo* model	*In vitro* model	Mechanism	Ref
EGCG	B16-F3m melanoma cells were injected into Balb/c mice	B16-F3m murine melanoma cells	*In vitro*: ↓colony formation, ↓cell spread, adhesion, migration & invasion, ↓ homotypic cell aggregation, ↓MMP-9 activity, ↓tyrosine phosphorylation of FAK, *In vivo*: ↓lung metastasis, ↑survival rate	[126]
EGCG	Xenograft model of B16BL6 mouse melanoma cells in C57BL/6 mice	B16-BL6 murine melanoma metastatic cell line	↓*In vitro* & *in vivo* cell growth, ↓DNA synthesis, delayed tumor growth, synergistic effect with cis-pt	[127]
Alpinumisoflavone	Xenograft model of melanoma using B16-F10 cells in C57BL/6 mice	A375 & SK-MEL-1 human melanoma cells & B16-F10 murine melanoma cell	*In vitro*: ↓cell proliferation & viability, ↓adhesion, migration, & invasion of human melanoma cells, ↑differentiation, ↓COX-2, SPHK1 by affecting miR-124 expression, *In vivo*: ↓lung metastasis	[128]
Amentoflavone	B16F-10 melanoma cells were injected into the tail vein of the C57BL/6 Mice	B16F-10 melanoma cell line	*In vitro*: ↓IL-1β, TNF-α, IL-6, GM-CSF & VEGF, ↓translocation of NF-κB subunits (p65, p50, & c-Rel), c-fos, ATF-2, & CREB, *In vivo*: ↑Survival, ↓ metastatic lung fibrosis & number of nodules, ↓lung fibrosis (via ↓lung uronic acid), ↓tumor burden (via ↓lung hexosamine), ↓sialic & GGT, ↑TIMP-1 & TIMP-2 expression, ↓GAPDH, ↓tumor mass, ↓IL-1β, TNF-α, IL-6, GM-CSF & VEGF, ↑IL-2, ↑NK cell activation	[129]
Amentoflavone	B16F-10 cells were injected into the lateral tail vein of C57BL/6 mice	B16F-10 melanoma cell culture	*In vitro*: ↓invasion, migration & proliferation of tumor cells, expressions, *In vivo*: ↓lung metastasis, ↓mRNA expressions of MMP-2, MMP-9, prolyl hydroxylase, lysyl oxidase, VEGF, ERK-1, & ERK-2, restored expression of STAT-1 & nm23 in lung tissues, ↓TNF-α, IL-1β, IL-6, & GM-CSF	[130]
Apigenin	Xenograft model of B16BL6 mouse melanoma cells in C57BL/6 mice	B16 B16-BL6 murine melanoma metastatic cell line	↓*In vitro* & *in vivo* cell growth, ↓DNA synthesis, ↓lung colonization, ↓cell invasion	[127]
Apigenin	B16F10 murine melanoma cells were injected into the tail vein of the C57BL/6 mice	Human melanoma A375 & G361 cell lines, murine melanoma B16F10 cells	*In vitro*: ↓phosphorylation of STAT3 at the tyrosine 705 (Tyr705) site,↓ phosphorylation of JAK2 & Src, ↓STAT3 nuclear localization, ↓STAT3 target genes (Twist1, MMP-2, MMP-9 & VEGF), ↑keratin 8 & E-cadherin mRNA expression, ↓epithelial-to-mesenchymal transition *In vivo*: ↓metastatic nodules, ↓lung metastasis, ↓tumor cell migration & invasion,	[131]
Apigenin Quercetin	Murine B16BL6 melanoma cells were injected into the lateral tail vein of C57BL/6 N mice	B16-BL6 murine melanoma metastatic cell line	*In vitro*: ↓TNF-α-induced VCAM-1 expression, ↓adhesion of melanoma cells to lung sections, *In vivo*: ↓lung metastasis, ↓cell adhesion to lung	[132]
Barbigerone	GFP transgenic zebrafish embryo B16F10 cells were implanted s.c. and i.v. on C57BL/6 mice	B16F10 cells	*In vitro*: ↓B16F10 cell proliferation, migration, & invasion, ↑apoptosis, ↓cell volume, ↓condensation of nuclear chromatin, ↓p38 MAPK, ↓ phosphorylation of ERK1/2, JNK1/2 & FAK, *In vivo*: ↓angiogenesis & tumor angiogenesis on zebrafish model, ↓blood vessel development in the trunk region, ↓tumor angiogenesis and tumor growth on mouse model, ↓ microvessel density, ↓lung metastasis	[133]
Biflorin	B16-F10 cells were injected into the tail vein of C57BL/6 mice	Mouse melanoma B16-F10 cell	*In vitro*: ↓cells adhesion to type I collagen, ↓migration and invasion, *In vivo*: ↓ lung metastasis & number of melanoma cells, ↑survival, ↑hemorrhage	[134]
Butein	B16F10 cells were slowly injected into the lateral tail vein of male C57BL/6 mouse	B16-BL6 murine melanoma metastatic cell line	*In vitro*: ↓cell proliferation & growth, ↓migration, ↓Akt, ERK1/2 & FAK phosphorylation, ↓mTOR & PI3K/ Akt, ↓p70S6K, 4E-BP1 & eIF4E phosphorylation, ↓VEGF *In vivo*: ↓lung metastasis	[135]
Catechin nanoformulation	WM266 human cancer cells xenotransplant in zebrafish embryos	WM266-4 human melanoma cell line	*In vitro*: ↓cell proliferation, ↓cell motility,↑cell death, ↑cell doubling time,↓ cell proliferation, ↓migration & invasion, *In vivo*: ↓cell proliferation, ↑cell doubling time, ↓migration, ↓tumor neo-angiogenesis	[136]
Cinnamic aldehyde	Xenograft model of A375 human melanoma cells in SCID-mouse	G-361, A375 & LOX human melanoma cells, Dermal neonatal foreskin Hs27 fibroblasts	↓Tumor size & growth, ↓*in vitro* cell proliferation with a moderate selectivity for cancerous cells, ↓DNA synthesis & cell cycle arrest in G1 phase, ↑ procaspase-3 cleavage & apoptosis, ↓invasion, ↑HMOX1, GPX2, SRXN1, TXNRD1, EGR1, DDIT3, & CDKN1A ↓NF-κB, IL-8 & TNFα	[137]
Curculigoside	B16F-10 melanoma cells were injected intravenously through lateral tail vein into the male C57BL/6 mice	-	↓Lung metastasis, ↑survival, ↑NK cell-mediated target cell lysis, ↑ADCC & ACC, ↑IL-2 & IFN-γ, ↓TNF-α, IL-1β, IL-6 & GM-CSF	[138]
Curcumin	B16F10 cells were injected iv into C57BL6 mice	B16F10 murine melanoma metastatic cell line	*In vitro*: ↓integrin-mediated binding of cells to ECM proteins, down regulation of both β_1, β_3, and α_v integrin subunits, ↓heterodimerization of $\alpha_5\beta_1$ and $\alpha_v\beta_3$ functional receptors, ↓invasion, ↓collagenase activity, ↑ tumor-suppressor genes TIMP-2, Nm23, & E-cadherin expression, ↓ pp125FAK expression, *In vivo*: ↓lung metastasis	[139]

(*continued on next page*)

Table 1 (*continued*)

1-Name	*In vivo* model	*In vitro* model	Mechanism	Ref
Curcumin	Xenograft model of B16BL6 mouse melanoma cells in C57BL/6 mice	B16-BL6 murine melanoma metastatic cell line	↓Cell growth *in vitro* but not *in vivo*, ↓DNA synthesis	[127]
Curcumin (free or as chitosan-coated nanoparticles)	B16F10 melanoma cells were injected intravenously into the tail vein of female C57BL/6 mice	B16-BL6 murine melanoma metastatic cell line	*In vitro*: ↓cell viability, ↑apoptosis, Disturbing mitochondrial membrane potential, ↓membrane integrity & fragmentation or condensation of nuclei, ↓ colony-forming ability, ↓migration ↓MMP-2 and MMP-9 activities, *In vivo*: ↓ cellular growth and proliferation, ↓number & size of lung metastatic nodules	[51]
Diosmin	B16F10 cells were injected into the lateral tail vein of female albino Swiss mice	-	↓Lung metastasis, ↓tumor implantation, ↓growth index, ↓invasion	[140]
Diosmin	Xenograft model of B16F10 in Swiss mice	-	↓Subpleural metastatic nodules, ↓invasion index, ↑implantation percentage	[141]
Fisetin	Female athymic nude mice were subcutaneously transplanted with A375 or SK-MEL-28 cells Athymic nude mice were iv injected with A375 cells in in the tail vein	Human malignant melanoma cells (A375) and SK-MEL-28 melanoma cells BRAF-mutated A375 & SK-MEL-28 melanoma cells	*In vitro*: ↓cell migration & invasion, ↓mesenchymal proteins (N-cadherin, vimentin and fibronectin) expression, ↑E-cadherin expression, ↓expression of Snail1, Twist1, Slug & ZEB1, expression, *In vivo*: ↓lung metastasis formation, ↓lung metastases, ↓EMT, ↓MMP-2 & -9 Synergism with sorfenib	[142]
Galangin	B16F10 cells were injected into the tail vein of female C57BL/6 J mice	B16F10 murine melanoma cells	*In vitro*: ↓viability, proliferation, adhesion, motility & migration, ↓F-actin rearrangement ↓migration, ↓FAK expression & activation, *In vivo*: ↓ number of nodules &, lung metastasis	[143]
Liquiritigenin + cisplatin	B16F10 cells were injected into the tail Vein of female C57 BL/6 black mice	B16F10 murine melanoma cells	*In vitro*: ↓cell viability, migration & invasion, ↓MMP-2 & MMP-9 activity & protein expression, ↑PTEN expression, regulation of PI3 K/AKT signaling pathway, *In vivo*: ↓serum MMP-2 & MMP-9, ↑PTEN expression, regulation of PI3 K/AKT signaling pathway, ↓lung weight & lung index, ↓lung metastasis	[144]
Magnolol	i.v. or s.c. injection of B16-BL6 melanoma cells into the C57BL/6 mice	B16-BL6A murine melanoma cell	*In vitro*: ↓cell invasion but not adhesion, had no effect on cell growth *In vivo*: ↓Primary tumor growth, ↓weight & size of the tumors, ↓lung metastasis	[145]
Naringenin, hesperitin	B16-F10 cells were injected iv into the tail vein of male C57BL/6 mice	B16-BL6 murine melanoma metastatic cell line	*In vitro*: ↓cell proliferation and growth, ↓intracellular levels of polyamines (SPD and SPM), ↑intracellular TGase activity, *In vivo*: ↓lung metastases, ↑ survival of mice, ↓invasion of melanoma cells Better efficacy with naringenin	[146]
Pterostilbene & quercetin (individually & in combination)	B16M-F10 cells were injected in the C57BL/6 J Mice mice were inoculated with control B16M-F10 or Bcl-2–overexpressing B16M-F10/Tet-Bcl-2 cells	B16M-F10 murine melanoma cell	*In vitro*: ↓tumor cell growth, cell cycle distribution (approximate percent of cells in ↑G0/G1, ↓S, and ↓G2/M phases), ↓cell adhesion (by pterostilbene but not quercetin), ↓number of penetrated colonies, ↑BAX expression, ↓Bcl-2 expression, intracellular Bcl-2 levels, VCAM *In vivo*: ↓density & volume of liver metastasis, ↓number of arrested cells ↑survival, Synergistic effects between the two compounds both *in vitro* & *in vivo*	[147]
Quercetin	C57BL/6 N mouse xenograft model of B16 cells in tail vein nu/nu BALB/c mouse xenograft model of A375 cells subcutaneously	Human melanoma A375 & A2058 cell lines	*In vitro*: ↓STAT3 phosphorylation & nuclear localization, ↓STAT3 signaling activation, down-regulation of STAT3 targeted genes Mcl-1, MMP-2, MMP-9 & VEGF, *In vivo*: ↓metastatic cells in lung	[148]
Quercetin	Xenograft model of B16BL6 mouse melanoma cells in C57BL/6 mice	B16-BL6 murine melanoma metastatic cell line	↓*In vitro* & *in vivo* cell growth, ↓DNA synthesis, delayed tumor growth, ↓ number of lung metastases, ↓lung colonization, ↓cell invasion, synergistic effect with cis-pt	[127]
Quercetin	_____	A375, A2058, sk-mel-2 & MeWo human melanoma cells	↓HGF-stimulated cell migration & invasion, ↓HGF/c-Met signaling pathway, ↓total c-Met expression levels, ↓c-Met phosphorylation & dimerization, ↓ mRNA expression levels of HGF, ↓activation of c-Met downstream molecules Gab1, FAK and PAK, ↓FAS expression	[149]
Resveratrol	B16 M(B16F10 subline) cells were intrasplenically injected into the syngeneic C57BL/6 J mice	B16 M cells (B16F10 subline), HSE hepatic sinusoidal endotheliumcells	*In vitro*: ↓HSE IL-18 secretion via inhibition of tumor-derived VEGF, ↓IL-18-induced VCAM-1 expression & microvascular cell adhesion, ↓p65 translocation & protein expression, ↓NF-κB activation *In vivo*: ↓hepatic metastasis, ↓hepatic IL-18 secretion,	[150]
Resveratrol	Xenograft model of B16BL6 mouse melanoma cells in C57BL/6 mice	B16-BL6 murine melanoma metastatic cell line	↓*In vitro* & *in vivo* cell growth, ↓DNA synthesis, delayed tumor growth	[127]
Resveratrol	Xenograft model of B16BL6 & B16F10 mouse melanoma cells in C57BL/6 mice	B16BL6 & B16F10 murine melanoma cell lines	*In vitro*: ↓Invasion & migration ↓Akt activity & expression, partial involvement of caspases, *In vivo*: ↓tumor size & growth, ↓lung metastasis,	[151]

(*continued on next page*)

Table 1 (*continued*)

1-Name	*In vivo* model	*In vitro* model	Mechanism	Ref
Tangeretin, diosmin rutin,	B16F10 cells were injected into the lateral tail vein of female albino Swiss mice	-	↓Lung metastasis (non-significant for tangeretin), ↓tumor implantation, ↓ invasion, ↓growth index	[152]
Wogonin	The B16-F10 melanoma cells were injected into the tail veins of male C57BL/6 mice	B16-F10 murine melanoma metastatic cell line	*In vitro*: ↓migration, adhesion & invasion, ↓expression of small G protein Ras & Rac1, ↓MMP-2, ↓migration (via ↓number of pseudopodia formated by F-actin), ↓ERK1/2 & AKT phosphorylation, ↓PI3K & PDK1, ↓IκBα & IKKα phosphorylation, ↓p65 nuclear (but not cytoplasmic) expression, ↓NF-κB signaling, ↓IGF-1 & TNF-α-induced invasion *In vivo*: ↓lung metastasis, ↓invasion	[153]

STAT3: Signal transducer and activator of transcription 3; VCAM-1: vascular cell adhesion molecule 1; ADCC: antibody-dependent cell-mediated cytotoxicity; FAK: Focal Adhesion Kinase; SPD: spermidine; SPM: spermine; TGase: transglutaminase; ECM: extracellular matrix; FN: fibronectin; LN: laminin; α5β1: fibronectin integrin receptor; αvβ3: vitronectin integrin receptor; TIMP-2:tissue inhibitor metalloproteinase; Nm23: nonmetastatic gene 23; EMT: epithelial to mesenchymal transition; IGF1: insulin like growth factor-1; PCNA: proliferating cell nuclear antigen; HMOX1: heme oxygenase-1; GPX2: glutathione peroxidase 2; SRXN1: sulfiredoxin 1 homolog; TXNRD1: thioredoxin reductase 1; EGR1: early growth response gene 1; DDIT3: DNA-damage-inducible transcript3; CDKN1A: cyclin-dependent kinase inhibitor 1A; GCLC: glutamate-cysteine ligase, catalytic subunit; NFκB: nuclear factor kappa B; ROS: reactive oxygen species; HGF: Hepatocyte growth factor; Gab1: associated binding protein 1; FAS: fatty acid synthase; PAK: p21-activated kinase; EMT: epithelial-to-mesenchymal transition; GAPDH: glyceraldehyde-phosphate dehydrogenase; IL: interleukin; TNF: tumor necrosis factor; GM-CSF: granulocyte monocyte–colony stimulating factor; VEGF: vascular endothelial growth factor; TIMP: tissue inhibitor of metalloprotease; NK cell: natural killer cell; ADCC: antibody-dependent cellular cytotoxicity; HSE: hepatic sinusoidal endothelium; ERK: extracellular signal regulated kinase; MMP: matrix metalloproteinase; implantation percentage: total area of metastasis × 100/total area of lobule; invasion index: total area of metastasis/mean area of metastasis; GOT: serum glutamic oxaloacetic transaminase; GPT: glutamic pyruvic transaminase

p38 signalling using wortmannin and other appropriate blockers may be an ideal attempt to inhibit that activity of TNF-α and phopshorylations of Akt [121].

9. Angiogenesis (VEGF)

Angiogenesis is a main physiological process in health and disease characterized by sprouting of novel blood vessels from pre-existing vessels. VEGF is a signal protein produced by cells that stimulates the formation of blood vessels. Certain polyphenol structures, as dihydroxyphenyl from the ethanolic extract from olive oil were shown to reduce proliferation of tumour cells and induce an abnormality in its angiogenesis. It inhibits IL-1β-induced expression of HIF-1α, microsomal prostaglandin-E synthase-1 (mPGEs-1) and VEGF by inhibiting the feedback loop between HIF-1α and mPGEs-1/PGE-2 signalling factors through suppression of the mPGEs-1/PGE-2/ VEGF and PGE-1/ ERK1/2/HIF-1α signalling cascades, resulting in blockade of cancer growth and associated angiogenesis [108,122].

Similar bioactivity was found with EGCG that suppresses the expression of VEGF dose dependently [122]. Curcumin also regulates the expression of target genes involved in cell survival and proliferation through modulation of multiple signalling pathways and VEGF, thus counteracting angiogenesis and affecting metastasis development [123].

10. Clinical perspective

Owing to the effectiveness of polyphenols in preclinical and in vitro surveys, clinical trials were conducted to illuminate the protective effects of polyphenols in skin cancer. In a randomized clinical examination, the antioxidative potential of tea polyphenols mixed with milks was assayed in 44 healthy volunteers. Decreased level of oxidative stress in treatment group compared to placebo was associated with improved integrity and texture of dermal tissues in aged and young subjects [124]. In view of increased level of oxidative stress in tissues exposed upon UV radiation, the photoptotective effects of chocolate flavonoids were also explored in clinical trials, however, due to probably the number of participants, the significant association of flavones was not accurately addressed and needs to further examination [125]. In this line, it is worthwhile to direct future clinical trials with adequate sample sizes and whole groups including healthy and patients. Further, discovering the underlying molecular mechanisms of polyphenols in clinical trials is required to conduct novel therapeutic strategies to combat skin cancer and ameliorate its outcomes. As discussed above, the low bioavailability and absorption of polyphenolics are the issues pertaining to the polyphenols. To get around the problems, now is the time to embrace nanotechnology based strategies such as nano-formulation, encapsulation and bioengineering in preclinical and clinical trials.

11. Conclusions

Supported by clear-cut evidences, modulation of cell proliferation, apoptosis and angiogenesis is one of the main goals of clinical trials to prevent and treat carcinogenesis. In this line, uncovering the molecular mechanisms of anticancer agents, such as certain identified polyphenolic structures, in induction of apoptosis, inhibition of cell proliferation and angiogenesis as well as cell cycle arrest seems to smooth the way in introducing the novel anticancer trials. Considering that cancer cells secret immunosuppressive factors to detach and migrate from local site as well as immunosuppressive effects of chemopreventive agents, activation of inflammatory responses seems to play the crucial role in cancer therapy. The anticancer mechanisms of the polyphenols study (phenolic acids as caffeic and rosmanic, flavonols as quercetine and myricetin, flavones as apigenin and luteolin, antocyanidines and protoantocyanidines) include different approaches to be

explored in further drug discovery research (Table 1). Among all, induction of antioxidant and apoptosis via induction of ASK-1, Caspase-3, JNK-p38 and pRb; suppression of cell cycle by upregulation of p21, Bcl2, and Bcl-x and down regulation of Bim, Bax, Puma ans Noxa; reduction of proliferation and angiogenesis through upregulation of EGFR, MAPK, mTOR, PI3K/Akt, FAK/PTK2, JAK/STAT, VEGF and HIF-1α (Table 1). It has been shown that several phenolic and polyphenolic compounds isolated from various plants have the potential to inhibit cellular proliferation, invasion and metastasis by modulating the expression of a number of inflammatory and cytokine genes including IL-6, IL-1, GM-CSF and TNF-α, IL-2, GM-CSF and INF-γ and IL-18 in melanoma models. In light of these evidence, unraveling the underlying anticancer molecular mechanism of these biocompounds bring a significant advantage in defeating carcinogenesis and metastasis of skin cells.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] S. Emmert, M.P. Schön, H.A. Haenssle, Molecular biology of basal and squamous cell carcinomas, Sunlight, vitamin D and skin cancer, Springer, 2014, pp. 234–252.
[2] R. Siegel, K. Miller, Jemal A. CA, a cancer journal for clinicians, Cancer Stat. 66 (2016) 7–30.
[3] G.P. Guy Jr, S.R. Machlin, D.U. Ekwueme, K.R. Yabroff, Prevalence and Costs of Skin Cancer Treatment in the US, 2002− 2006 and 2007− 2011, American journal of preventive medicine 48 (2) (2015) 183–187.
[4] Skin cancer: an overview of epidemiology and risk factors, in: R. Gordon (Ed.), Seminars in oncology nursing, Elsevier, 2013.
[5] J. Liu, M. Fukunaga-Kalabis, L. Li, M. Herlyn, Developmental pathways activated in melanocytes and melanoma, Archives of biochemistry and biophysics 563 (2014) 13–21.
[6] C. Michaloglou, L.C. Vredeveld, M.S. Soengas, C. Denoyelle, T. Kuilman, C.M. Van Der Horst, et al., BRAF E600-associated senescence-like cell cycle arrest of human naevi, Nature. 436 (7051) (2005) 720.
[7] J. Paluncic, Z. Kovacevic, P.J. Jansson, D. Kalinowski, A.M. Merlot, Huang ML-H, et al., Roads to melanoma: Key pathways and emerging players in melanoma progression and oncogenic signaling, Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 1863 (4) (2016) 770–784.
[8] M. Simões, J. Sousa, A. Pais, Skin cancer and new treatment perspectives: A review, Cancer letters 357 (1) (2015) 8–42.
[9] M. Hosein Farzaei, R. Bahramsoltani, R. Rahimi, Phytochemicals as adjunctive with conventional anticancer therapies, Current pharmaceutical design 22 (27) (2016) 4201–4218.
[10] H. Khan, H. Ullah, Castilho PCMF, A.S. Gomila, G. D'Onofrio, R. Filosa, F. Wang, S.M. Nabavi, M. Daglia, A.S. Silva, K.R.R. Rengasamy, J.Y. Ou, X.B. Zou, J.B. Xiao, Cao H Targeting NF-κB signaling pathway in cancer by dietary polyphenols, Critical Reviews in Food Science and Nutrition (2019), https://doi.org/10.1080/10408398.2019.1661827.
[11] V. Jones, S.K. Katiyar, Emerging phytochemicals for prevention of melanoma invasion, Cancer letters 335 (2) (2013) 251–258.
[12] L. Chen, H. Cao, J.B. Xiao, Polyphenols: absorption, bioavailability and metabolomics. In Polyphenols: Properties, Recovery, and Applications, Elsevier, 2018, pp. 45–68 ISBN: 978-0-12-813572-3.
[13] I.R. Record, J.M. Lane, Simulated intestinal digestion of green and black teas, Food Chemistry. 73 (4) (2001) 481–486.
[14] L.Y. Rios, R.N. Bennett, S.A. Lazarus, C. Rémésy, A. Scalbert, G. Williamson, Cocoa procyanidins are stable during gastric transit in humans, The American journal of clinical nutrition 76 (5) (2002) 1106–1110.
[15] S. Stoupi, G. Williamson, F. Viton, D. Barron, L.J. King, J.E. Brown, et al., In vivo bioavailability, absorption, excretion, and pharmacokinetics of [14C] procyanidin B2 in male rats, Drug Metabolism and Disposition. 38 (2) (2010) 287–291.
[16] C.H. Weinert, S. Wiese, H.M. Rawel, T. Esatbeyoglu, P. Winterhalter, T. Homann, et al., Methylation of catechins and procyanidins by rat and human catechol-O-methyltransferase: metabolite profiling and molecular modeling studies, Drug Metabolism and Disposition. 40 (2) (2012) 353–359.
[17] G. Kuhnle, J.P. Spencer, H. Schroeter, B. Shenoy, E.S. Debnam, S.K.S. Srai, et al., Epicatechin and catechin are O-methylated and glucuronidated in the small intestine, Biochemical and biophysical research communications 277 (2) (2000) 507–512.
[18] S.K. Katiyar, Green tea prevents non-melanoma skin cancer by enhancing DNA repair, Archives of biochemistry and biophysics 508 (2) (2011) 152–158.
[19] F. Orallo, Comparative studies of the antioxidant effects of cis-and trans-resveratrol, Current medicinal chemistry 13 (1) (2006) 87–98.
[20] L. Frémont, Biological effects of resveratrol, Life Sci. 66 (8) (2000) 663–673.
[21] V.D. Bokkenheuser, C. Shackleton, J. Winter, Hydrolysis of dietary flavonoid glycosides by strains of intestinal Bacteroides from humans, Biochem J. 248 (3) (1987) 953–956.
[22] T. Ozdal, D. Sela, J.B. Xiao, D. Boyacioglu, F. Chen, E. Capanoglu, The reciprocal effects of polyphenols on the gut microbiota community and bioaccessibility, Nutrients 8 (2) (2016) 78.
[23] C. Manach, A. Scalbert, C. Morand, C. Rémésy, L. Jiménez, Polyphenols: food sources and bioavailability, The American journal of clinical nutrition 79 (5) (2004) 727–747.
[24] V. Curti, A. Di Lorenzo, M. Da Crema, J.B. Xiao, S.M. Nabavi, M. Daglia, In vitro polyphenol effects on apoptosis: an update of literature data, Seminars in Cancer Biology 46 (2017) 119–131.
[25] J. Shi, F. Liu, W. Zhang, X. Liu, B. Lin, X. Tang, Epigallocatechin-3-gallate inhibits nicotine-induced migration and invasion by the suppression of angiogenesis and epithelial-mesenchymal transition in non-small cell lung cancer cells, Oncology reports 33 (6) (2015) 2972–2980.
[26] J.B. Xiao, Dietary flavonoid aglycones and their glycosides: Which show better biological significance? Critical Reviews in Food Science and Nutrition 57 (2017) 1874–1905.
[27] F. Li, S. Li, H.-B. Li, G.-F. Deng, W.-H. Ling, X.-R. Xu, Antiproliferative activities of tea and herbal infusions, Food & function 4 (4) (2013) 530–538.
[28] H. Khan, M. Reale, H. Ullah, A. Sureda, S. Tejada, Y. Wang, Z.J. Zhang, J.B. Xiao, Anti-cancer effects of polyphenols via targeting p53 signaling pathway: updates and future directions, Biotechnology Advances (2019), https://doi.org/10.1016/j.biotechadv.2019.04.007.
[29] B.B. Aggarwal, S. Shishodia, Resveratrol: A Polyphenol for All Seasons, Resveratrol in Health and Disease, CRC Press, 2005, pp. 31–46.
[30] A. Bishayee, Cancer prevention and treatment with resveratrol: from rodent studies to clinical trials, Cancer prevention research (2009) 1940–6207 CAPR-08-0160.
[31] N. Kalra, P. Roy, S. Prasad, Y. Shukla, Resveratrol induces apoptosis involving mitochondrial pathways in mouse skin tumorigenesis, Life sciences 82 (7-8) (2008) 348–358.
[32] F. Afaq, V.M. Adhami, N. Ahmad, Prevention of short-term ultraviolet B radiation-mediated damages by resveratrol in SKH-1 hairless micez.star; Toxicology and applied pharmacology 186 (1) (2003) 28–37.
[33] S. Reagan-Shaw, F. Afaq, M.H. Aziz, N. Ahmad, Modulations of critical cell cycle regulatory events during chemoprevention of ultraviolet B-mediated responses by resveratrol in SKH-1 hairless mouse skin, Oncogene. 23 (30) (2004) 5151.
[34] M.H. Aziz, F. Afaq, N. Ahmad, Prevention of Ultraviolet-B Radiation Damage by Resveratrol in Mouse Skin Is Mediated via Modulation in Survivin¶, Photochemistry and photobiology 81 (1) (2005) 25–31.
[35] M.H. Aziz, S. Reagan-Shaw, J. Wu, B.J. Longley, N. Ahmad, Chemoprevention of skin cancer by grape constituent resveratrol: relevance to human disease? The FASEB journal 19 (9) (2005) 1193–1195.
[36] S. Banerjee, C. Bueso-Ramos, B.B. Aggarwal, Suppression of 7, 12-dimethylbenz (a) anthracene-induced mammary carcinogenesis in rats by resveratrol: role of nuclear factor-κB, cyclooxygenase 2, and matrix metalloprotease 9, Cancer research. 62 (17) (2002) 4945–4954.
[37] T. Whitsett, M. Carpenter, C.A. Lamartiniere, Resveratrol, but not EGCG, in the diet suppresses DMBA-induced mammary cancer in rats, Journal of carcinogenesis. 5 (2006) 15.
[38] K.P. Bhat, D. Lantvit, K. Christov, R.G. Mehta, R.C. Moon, J.M. Pezzuto, Estrogenic and antiestrogenic properties of resveratrol in mammary tumor models, Cancer research 61 (20) (2001) 7456–7463.
[39] S. Garvin, K. Öllinger, C. Dabrosin, Resveratrol induces apoptosis and inhibits angiogenesis in human breast cancer xenografts in vivo, Cancer letters 231 (1) (2006) 113–122.
[40] M. Provinciali, F. Re, A. Donnini, F. Orlando, B. Bartozzi, G. Di Stasio, et al., Effect of resveratrol on the development of spontaneous mammary tumors in HER-2/neu transgenic mice, International journal of cancer 115 (1) (2005) 36–45.
[41] H. Lee, P. Zhang, A. Herrmann, C. Yang, H. Xin, Z. Wang, et al., Acetylated STAT3 is crucial for methylation of tumor-suppressor gene promoters and inhibition by resveratrol results in demethylation, Proceedings of the National Academy of Sciences 109 (20) (2012) 7765–7769.
[42] D. Chen, S.B. Wan, H. Yang, J. Yuan, T.H. Chan, Q.P. Dou, EGCG, green tea polyphenols and their synthetic analogs and prodrugs for human cancer prevention and treatment, Advances in clinical chemistry 53 (2011) 155.
[43] S.K. Mantena, S.M. Meeran, C.A. Elmets, S.K. Katiyar, Orally administered green tea polyphenols prevent ultraviolet radiation-induced skin cancer in mice through activation of cytotoxic T cells and inhibition of angiogenesis in tumors, The Journal of nutrition 135 (12) (2005) 2871–2877.
[44] A. Facchini, B. Zanella, C. Stefanelli, C. Guarnieri, F. Flamigni, Effect of green tea extract on the induction of ornithine decarboxylase and the activation of extracellular signal-regulated kinase in bladder carcinoma ECV304 cells, Nutrition and cancer 47 (1) (2003) 104–111.
[45] S.-C. Lee, W.-K. Chan, T.-W. Lee, W.-H. Lam, X. Wang, T.-H. Chan, et al., Effect of a prodrug of the green tea polyphenol (-)-epigallocatechin-3-gallate on the growth of androgen-independent prostate cancer in vivo, Nutrition and cancer 60 (4) (2008) 483–491.
[46] S. Bettuzzi, M. Brausi, F. Rizzi, G. Castagnetti, G. Peracchia, A. Corti, Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study, Cancer research 66 (2) (2006) 1234–1240.

[47] A. Jatoi, N. Ellison, P.A. Burch, J.A. Sloan, S.R. Dakhil, P. Novotny, et al., A phase II trial of green tea in the treatment of patients with androgen independent metastatic prostate carcinoma, Cancer: Interdisciplinary International Journal of the American Cancer Society. 97 (6) (2003) 1442–1446.
[48] I. Brouet, H. Ohshima, Curcumin, an anti-tumor promoter and anti-inflammatory agent, inhibits induction of nitric oxide synthase in activated macrophages, Biochemical and biophysical research communications 206 (2) (1995) 533–540.
[49] A.B. Kunnumakkara, P. Anand, B.B. Aggarwal, Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins, Cancer letters. 269 (2) (2008) 199–225.
[50] A. Mukhopadhyay, C. Bueso-Ramos, D. Chatterjee, P. Pantazis, B.B. Aggarwal, Curcumin downregulates cell survival mechanisms in human prostate cancer cell lines, Oncogene. 20 (52) (2001) 7597.
[51] G. Loch-Neckel, L. Santos-Bubniak, L. Mazzarino, A.V. Jacques, B. Moccelin, M.C. Santos-Silva, et al., Orally administered chitosan-coated polycaprolactone nanoparticles containing curcumin attenuate metastatic melanoma in the lungs, Journal of pharmaceutical sciences 104 (10) (2015) 3524–3534.
[52] H. Amawi, C. Ashby, T. Samuel, R. Peraman, A. Tiwari, Polyphenolic nutrients in cancer chemoprevention and metastasis: role of the Epithelial-to-Mesenchymal (EMT) pathway, Nutrients. 9 (8) (2017) 911.
[53] D. Avtanski, L. Poretsky, Phyto-polyphenols as potential inhibitors of breast cancer metastasis, Molecular Medicine. 24 (1) (2018) 29.
[54] S. Balasubramanian, T. Efimova, R.L. Eckert, Green tea polyphenol stimulates a Ras, MEKK1, MEK3, and p38 cascade to increase activator protein 1 factor-dependent involucrin gene expression in normal human keratinocytes, Journal of Biological Chemistry. 277 (3) (2002) 1828–1836.
[55] L. Gong, Y. Li, A. Nedeljkovic-Kurepa, F.H. Sarkar, Inactivation of NF-κB by genistein is mediated via Akt signaling pathway in breast cancer cells, Oncogene. 22 (30) (2003) 4702.
[56] T. Singh, S.K. Katiyar, Green tea polyphenol,(−)-epigallocatechin-3-gallate, induces toxicity in human skin cancer cells by targeting β-catenin signaling, Toxicology and applied pharmacology. 273 (2) (2013) 418–424.
[57] V.S. Thakur, K. Gupta, S. Gupta, Green tea polyphenols causes cell cycle arrest and apoptosis in prostate cancer cells by suppressing class I histone deacetylases, Carcinogenesis. 33 (2) (2011) 377–384.
[58] M. Holczer, B. Besze, V. Zámbó, M. Csala, G. Bánhegyi, O. Kapuy, Epigallocatechin-3-Gallate (EGCG) Promotes Autophagy-Dependent Survival via Influencing the Balance of mTOR-AMPK Pathways upon Endoplasmic Reticulum Stress, Oxidative medicine and cellular longevity 2018 (2018).
[59] N. Ahmad, V.M. Adhami, S. Gupta, P. Cheng, H. Mukhtar, Role of the retinoblastoma (PRB)–E2F/DP pathway in cancer chemopreventive effects of green tea polyphenol epigallocatechin-3-gallate, Archives of biochemistry and biophysics 398 (1) (2002) 125–131.
[60] L.A. Checkley, O. Rho, T. Moore, S. Hursting, J. DiGiovanni, Rapamycin is a potent inhibitor of skin tumor promotion by 12-O-tetradecanoylphorbol-13-acetate, Cancer prevention research 4 (7) (2011) 1011–1020.
[61] M. Athar, L. Kopelovich, Rapamycin and mTORC1 inhibition in the mouse: skin cancer prevention, Cancer prevention research 4 (7) (2011) 957–961.
[62] J.W. de Fijter, Cancer and mTOR inhibitors in transplant recipients, Transplantation. 101 (1) (2017) 45–55.
[63] S.K. Katiyar, F. Afaq, K. Azizuddin, H. Mukhtar, Inhibition of UVB-induced oxidative stress-mediated phosphorylation of mitogen-activated protein kinase signaling pathways in cultured human epidermal keratinocytes by green tea polyphenol (−)-epigallocatechin-3-gallate, Toxicology and applied pharmacology 176 (2) (2001) 110–117.
[64] J.M. García-Martínez, J. Moran, R.G. Clarke, A. Gray, S.C. Cosulich, C.M. Chresta, et al., Ku-0063794 is a specific inhibitor of the mammalian target of rapamycin (mTOR), Biochemical Journal. 421 (1) (2009) 29–42.
[65] N. Pećina-Šlaus, Tumor suppressor gene E-cadherin and its role in normal and malignant cells, Cancer cell international 3 (1) (2003) 17.
[66] E. Turrini, L. Ferruzzi, C. Fimognari, Potential effects of pomegranate polyphenols in cancer prevention and therapy, Oxidative medicine and cellular longevity 2015 (2015).
[67] S.D. Sharma, S.K. Katiyar, Dietary grape seed proanthocyanidins inhibit UVB-induced cyclooxygenase-2 expression and other inflammatory mediators in UVB-exposed skin and skin tumors of SKH-1 hairless mice, Pharmaceutical research 27 (6) (2010) 1092–1102.
[68] N. Zeng, T. Hongbo, Y. Xu, M. Wu, Y. Wu, Anticancer activity of caffeic acid n-butyl ester against A431 skin carcinoma cell line occurs via induction of apoptosis and inhibition of the mTOR/PI3K/AKT signaling pathway, Molecular medicine reports 17 (4) (2018) 5652–5657.
[69] P.-Y. Zhang, Polyphenols in health and disease, Cell biochemistry and biophysics 73 (3) (2015) 649–664.
[70] Z. Estrov, S. Shishodia, S. Faderl, D. Harris, Q. Van, H.M. Kantarjian, et al., Resveratrol blocks interleukin-1β–induced activation of the nuclear transcription factor NF-κB, inhibits proliferation, causes S-phase arrest, and induces apoptosis of acute myeloid leukemia cells, Blood. 102 (3) (2003) 987–995.
[71] Z. Wu, B. Liu, J. Liu, Q. Zhang, J. Liu, N. Chen, et al., Resveratrol inhibits the proliferation of human melanoma cells by inducing G1/S cell cycle arrest and apoptosis, Molecular medicine reports 11 (1) (2015) 400–404.
[72] Yang T-Y Yu M-H, H.-H. Ho, H.-P. Huang, K.-C. Chan, C.-J. Wang, Mulberry Polyphenol Extract Inhibits FAK/Src/PI3K Complex and Related Signaling To Regulate the Migration in A7r5 Cells, Journal of agricultural and food chemistry 66 (15) (2018) 3860–3869.
[73] S. Lamy, N. Akla, A. Ouanouki, S. Lord-Dufour, R. Béliveau, Diet-derived polyphenols inhibit angiogenesis by modulating the interleukin-6/STAT3 pathway, Experimental cell research 318 (13) (2012) 1586–1596.
[74] T. Kumamoto, M. Fujii, D.-X. Hou, Myricetin directly targets JAK1 to inhibit cell transformation, Cancer letters 275 (1) (2009) 17–26.
[75] C. Rajagopal, M.B. Lankadasari, J.M. Aranjani, K. Harikumar, Targeting oncogenic transcription factors by polyphenols: A novel approach for cancer therapy, Pharmacological research (2018).
[76] J. Michaud-Levesque, N. Bousquet-Gagnon, R. Béliveau, Quercetin abrogates IL-6/STAT3 signaling and inhibits glioblastoma cell line growth and migration, Experimental cell research 318 (8) (2012) 925–935.
[77] S. Momtaz, K. Niaz, F. Maqbool, M. Abdollahi, L. Rastrelli, S.M. Nabavi, STAT3 targeting by polyphenols: Novel therapeutic strategy for melanoma, Biofactors. 43 (3) (2017) 347–370.
[78] M. Masuda, M. Suzui, J.T. Lim, I.B. Weinstein, Epigallocatechin-3-gallate inhibits activation of HER-2/neu and downstream signaling pathways in human head and neck and breast carcinoma cells, Clinical Cancer Research. 9 (9) (2003) 3486–3491.
[79] M.K. Pandey, B. Sung, K.S. Ahn, B.B. Aggarwal, Butein suppresses constitutive and inducible signal transducer and activator of transcription (STAT) 3 activation and STAT3-regulated gene products through the induction of a protein tyrosine phosphatase SHP-1, Molecular pharmacology 75 (3) (2009) 525–533.
[80] R. Kannaiyan, H.S. Hay, P. Rajendran, F. Li, M.K. Shanmugam, S. Vali, et al., Celastrol inhibits proliferation and induces chemosensitization through down-regulation of NF-κB and STAT3 regulated gene products in multiple myeloma cells, British journal of pharmacology 164 (5) (2011) 1506–1521.
[81] P.K. Vayalil, C.A. Elmets, S.K. Katiyar, Treatment of green tea polyphenols in hydrophilic cream prevents UVB-induced oxidation of lipids and proteins, depletion of antioxidant enzymes and phosphorylation of MAPK proteins in SKH-1 hairless mouse skin, Carcinogenesis. 24 (5) (2003) 927–936.
[82] P. OyetakinWhite, H. Tribout, E. Baron, Protective mechanisms of green tea polyphenols in skin, Oxidative medicine and cellular longevity 2012 (2012).
[83] S.-H. Kim, C.-D. Jun, K. Suk, B.-J. Choi, H. Lim, S. Park, et al., Gallic acid inhibits histamine release and pro-inflammatory cytokine production in mast cells, Toxicological Sciences. 91 (1) (2005) 123–131.
[84] M. Gu, R.P. Singh, S. Dhanalakshmi, S. Mohan, R. Agarwal, Differential effect of silibinin on E2F transcription factors and associated biological events in chronically UVB-exposed skin versus tumors in SKH-1 hairless mice, Molecular cancer therapeutics 5 (8) (2006) 2121–2129.
[85] F. Afaq, M. Saleem, C.G. Krueger, J.D. Reed, H. Mukhtar, Anthocyanin-and hydrolyzable tannin-rich pomegranate fruit extract modulates MAPK and NF-κB pathways and inhibits skin tumorigenesis in CD-1 mice, International Journal of Cancer. 113 (3) (2005) 423–433.
[86] A.M. Aliper, V.P. Frieden-Korovkina, A. Buzdin, S.A. Roumiantsev, A. Zhavoronkov, A role for G-CSF and GM-CSF in nonmyeloid cancers, Cancer medicine 3 (4) (2014) 737–746.
[87] M.M. Loesch, A.E. Collier, D.H. Southern, R.E. Ward, S.S. Tholpady, D.A. Lewis, et al., Insulin-like growth factor-1 receptor regulates repair of ultraviolet B-induced DNA damage in human keratinocytes in vivo, Molecular oncology 10 (8) (2016) 1245–1254.
[88] J. McLarty, R.L. Bigelow, M. Smith, D. Elmajian, M. Ankem, J.A. Cardelli, Tea polyphenols decrease serum levels of prostate-specific antigen, hepatocyte growth factor, and vascular endothelial growth factor in prostate cancer patients and inhibit production of hepatocyte growth factor and vascular endothelial growth factor in vitro, Cancer prevention research. (2009) 1940–6207 CAPR-08-0167.
[89] J.M. Roda, Y. Wang, L.A. Sumner, G.S. Phillips, C.B. Marsh, T.D. Eubank, Stabilization of HIF-2α induces sVEGFR-1 production from tumor-associated macrophages and decreases tumor growth in a murine melanoma model, The Journal of Immunology. (2012) 1103817.
[90] H. Kim, J. Park, K.-H. Tak, S.Y. Bu, E. Kim, Chemopreventive effects of curcumin on chemically induced mouse skin carcinogenesis in BK5. insulin-like growth factor-1 transgenic mice, In Vitro Cellular & Developmental Biology-Animal. 50 (9) (2014) 883–892.
[91] R.-C. Ji, Y. Eshita, Rapamycin inhibition of CFA-induced lymphangiogenesis in PLN is independent of mast cells, Molecular biology reports 41 (4) (2014) 2217–2228.
[92] M. Guba, M. Yezhelyev, M.E. Eichhorn, G. Schmid, I. Ischenko, A. Papyan, et al., Rapamycin induces tumor-specific thrombosis via tissue factor in the presence of VEGF, Blood. 105 (11) (2005) 4463–4469.
[93] K.S. Siveen, S. Sikka, R. Surana, X. Dai, J. Zhang, A.P. Kumar, et al., Targeting the STAT3 signaling pathway in cancer: role of synthetic and natural inhibitors, Biochimica et Biophysica Acta (BBA)-reviews on cancer 1845 (2) (2014) 136–154.
[94] M.-T. Lin, M.-L. Yen, C.-Y. Lin, M.-L. Kuo, Inhibition of vascular endothelial growth factor-induced angiogenesis by resveratrol through interruption of Src-dependent vascular endothelial cadherin tyrosine phosphorylation, Molecular pharmacology 64 (5) (2003) 1029–1036.
[95] P. Pittayapruek, J. Meephansan, O. Prapapan, M. Komine, M. Ohtsuki, Role of matrix metalloproteinases in photoaging and photocarcinogenesis, International journal of molecular sciences 17 (6) (2016) 868.
[96] F. Afaq, M.A. Zaid, N. Khan, M. Dreher, H. Mukhtar, Protective effect of pomegranate-derived products on UVB-mediated damage in human reconstituted skin, Experimental dermatology 18 (6) (2009) 553–561.
[97] F. Afaq, S. K Katiyar, Polyphenols: skin photoprotection and inhibition of photocarcinogenesis, Mini reviews in medicinal chemistry 11 (14) (2011) 1200–1215.
[98] W. Gao, P. Lin, E. Hwang, Y. Wang, Z. Yan, H.T. Ngo, et al., Pterocarpus santalinus L. Regulated Ultraviolet B Irradiation-induced Procollagen Reduction and Matrix Metalloproteinases Expression Through Activation of TGF-β/Smad and Inhibition of the MAPK/AP-1 Pathway in Normal Human Dermal Fibroblasts,

Photochemistry and photobiology 94 (1) (2018) 139–149.
[99] H.-M. Chiang, H.-C. Chen, H.-H. Chiu, C.-W. Chen, S.-M. Wang, K.-C. Wen, Neonauclea reticulata (Havil.) Merr stimulates skin regeneration after UVB exposure via ROS scavenging and modulation of the MAPK/MMPs/collagen pathway, Evidence-Based Complementary and Alternative Medicine. 2013 (2013).
[100] N. Banerjee, H. Kim, S. Talcott, S. Mertens-Talcott, Pomegranate polyphenolics suppressed azoxymethane-induced colorectal aberrant crypt foci and inflammation: possible role of miR-126/VCAM-1 and miR-126/PI3K/AKT/mTOR, Carcinogenesis. 34 (12) (2013) 2814–2822.
[101] Z. Hou, J.D. Lambert, K.-V. Chin, C.S. Yang, Effects of tea polyphenols on signal transduction pathways related to cancer chemoprevention, Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. 555 (1-2) (2004) 3–19.
[102] N. Philips, S. Auler, R. Hugo, S. Gonzalez, Beneficial regulation of matrix metalloproteinases for skin health, Enzyme research 2011 (2011).
[103] M. Zhang, E. Hwang, P. Lin, W. Gao, H.T. Ngo, T.-H. Yi, Prunella vulgaris L. Exerts a Protective Effect Against Extrinsic Aging through NF-κB, MAPKs, AP-1, and TGF-β/Smad Signaling Pathways in UVB-Aged Normal Human Dermal Fibroblasts, Rejuvenation research. (2018).
[104] Y.-A. Song, Y.-L. Park, S.-H. Yoon, K.-Y. Kim, S.-B. Cho, W.-S. Lee, et al., Black tea polyphenol theaflavin suppresses LPS-induced ICAM-1 and VCAM-1 expression via blockage of NF-κB and JNK activation in intestinal epithelial cells, Inflammation Research. 60 (5) (2011) 493–500.
[105] W. Liu, S. Wu, The roles of Akt and NOSs in regulation of VLA-4-mediated melanoma cell adhesion to endothelial VCAM-1 after UVB-irradiation, Archives of biochemistry and biophysics 508 (2) (2011) 192–197.
[106] H. Yin, X. Shi, H. Wang, W. Jin, Y. Li, Y. Fu, Photodynamic therapy targeting VCAM-1-expressing human umbilical vein endothelial cells using a PpIX–VCAM-1 binding peptide–quantum dot conjugate, RSC Advances. 7 (80) (2017) 50562–50570.
[107] F.J. Sulzmaier, C. Jean, D.D. Schlaepfer, FAK in cancer: mechanistic findings and clinical applications, Nature reviews cancer 14 (9) (2014) 598.
[108] Q. Zhou, L.L. Bennett, S. Zhou, Multifaceted ability of naturally occurring polyphenols against metastatic cancer, Clinical and Experimental Pharmacology and Physiology 43 (4) (2016) 394–409.
[109] C.-C. Huang, C.-H. Hung, C.-C. Chen, S.-H. Kao, C.-J. Wang, Hibiscus sabdariffa polyphenol-enriched extract inhibits colon carcinoma metastasis associating with FAK and CD44/c-MET signaling, Journal of Functional Foods. 48 (2018) 542–550.
[110] C.-C. Su, C.-J. Wang, K.-H. Huang, Y.-J. Lee, W.-M. Chan, Y.-C. Chang, Anthocyanins from Hibiscus sabdariffa calyx attenuate in vitro and in vivo melanoma cancer metastasis, Journal of Functional Foods. 48 (2018) 614–631.
[111] S. Lupinacci, A. Perri, G. Toteda, D. Vizza, F. Puoci, O. Parisi, et al., Olive leaf extract counteracts epithelial to mesenchymal transition process induced by peritoneal dialysis, through the inhibition of TGFβ1 signaling, Cell biology and toxicology. (2018) 1–15.
[112] Y.-C. Chang, P.-N. Chen, S.-C. Chu, C.-Y. Lin, W.-H. Kuo, Y.-S. Hsieh, Black tea polyphenols reverse epithelial-to-mesenchymal transition and suppress cancer invasion and proteases in human oral cancer cells, Journal of agricultural and food chemistry 60 (34) (2012) 8395–8403.
[113] J. Loureiro, P. Sandoval, G. del Peso, G. Gónzalez-Mateo, V. Fernández-Millara, B. Santamaria, et al., Tamoxifen ameliorates peritoneal membrane damage by blocking mesothelial to mesenchymal transition in peritoneal dialysis, PloS one 8 (4) (2013) e61165.
[114] X. Zhang, X. Liu, S. Kang, C. Liu, Y. Hao, Resveratrol enhances the effects of ALA-PDT on skin squamous cells A431 through p38/MAPK signaling pathway, Cancer Biomarkers. (2018) 1–7 (Preprint).
[115] L. Castillo-Pichardo, L.A. Cubano, S. Dharmawardhane, Dietary grape polyphenol resveratrol increases mammary tumor growth and metastasis in immunocompromised mice, BMC complementary and alternative medicine 13 (1) (2013) 6.
[116] A. Ukil, S. Maity, P.K. Das, Protection from experimental colitis by theaflavin-3, 3′-digallate correlates with inhibition of IKK and NF-κB activation, British journal of pharmacology. 149 (1) (2006) 121–131.
[117] U. Bhattacharya, B. Halder, S. Mukhopadhyay, A.K. Giri, Role of oxidation--triggered activation of JNK and p38 MAPK in black tea polyphenols induced apoptotic death of A375 cells, Cancer Science. 100 (10) (2009) 1971–1978.
[118] H. Zulkipli, G.R.A. Froemming, A.M. Ismail, Comparative effects between Green Tea and Black Tea polyphenols in suppressing adverse effects of TNF-α induced inflammation in osteoblasts, Journal of Engineering and Applied Sciences. 13 (6) (2018) 1552–1560.
[119] X. Zhao, P. Sun, G. Li, R. Yi, Y. Qian, K.-Y. Park, Polyphenols in Kuding tea help prevent HCl/ethanol-induced gastric injury in mice, Food & function 9 (3) (2018) 1713–1725.
[120] E.T. Callcott, K. Thompson, P. Oli, C.L. Blanchard, A.B. Santhakumar, Coloured rice-derived polyphenols reduce lipid peroxidation and pro-inflammatory cytokines ex vivo, Food & function 9 (10) (2018) 5169–5175.
[121] A. Faurschou, R. Gniadecki, TNF-α stimulates Akt by a distinct aPKC-dependent pathway in premalignant keratinocytes, Experimental dermatology 17 (12) (2008) 992–997.
[122] E. Terzuoli, S. Donnini, A. Giachetti, M.A. Iñiguez, M. Fresno, G. Melillo, et al., Inhibition of hypoxia inducible factor-1α by dihydroxyphenylethanol, a product from olive oil, blocks microsomal prostaglandin-E synthase-1/vascular endothelial growth factor expression and reduces tumor angiogenesis, Clinical Cancer Research. (2010) 1078-0432. CCR-10-156.
[123] M.-H. Oak, J. El Bedoui, V.B. Schini-Kerth, Antiangiogenic properties of natural polyphenols from red wine and green tea, The Journal of nutritional biochemistry 16 (1) (2005) 1–8.
[124] H.-F. Chiu, T.-Y. Lin, Y.-C. Shen, K. Venkatakrishnan, C.-K. Wang, Improvement of green tea polyphenol with milk on skin with respect to antioxidation in healthy adults: a double-blind placebo-controlled randomized crossover clinical trial, Food & function 7 (2) (2016) 893–901.
[125] J.A. Mogollon, C. Boivin, S. Lemieux, C. Blanchet, J. Claveau, S. Dodin, Chocolate flavanols and skin photoprotection: a parallel, double-blind, randomized clinical trial, Nutrition journal. 13 (1) (2014) 66.
[126] J.D. Liu, S.H. Chen, C.L. Lin, S.H. Tsai, Y.C. Liang, Inhibition of melanoma growth and metastasis by combination with (−)-epigallocatechin-3-gallate and dacarbazine in mice, Journal of cellular biochemistry 83 (4) (2001) 631–642.
[127] S. Caltagirone, C. Rossi, A. Poggi, F.O. Ranelletti, P.G. Natali, M. Brunetti, et al., Flavonoids apigenin and quercetin inhibit melanoma growth and metastatic potential, International Journal of Cancer. 87 (4) (2000) 595–600.
[128] M. Gao, Y. Chang, X. Wang, C. Ban, F. Zhang, Reduction of COX-2 through modulating miR-124/SPHK1 axis contributes to the antimetastatic effect of alpinumisoflavone in melanoma, American journal of translational research 9 (3) (2017) 986.
[129] C. Guruvayoorappan, G. Kuttan, Effect of amentoflavone on the inhibition of pulmonary metastasis induced by B16F-10 melanoma cells in C57BL/6 mice, Integrative cancer therapies 6 (2) (2007) 185–197.
[130] C. Guruvayoorappan, G. Kuttan, Amentoflavone inhibits experimental tumor metastasis through a regulatory mechanism involving MMP-2, MMP-9, prolyl hydroxylase, lysyl oxidase, VEGF, ERK-1, ERK-2, STAT-1, NM23 and cytokines in lung tissues of C57BL/6 mice, Immunopharmacology and immunotoxicology 30 (4) (2008) 711–727.
[131] H.H. Cao, J.H. Chu, H.Y. Kwan, T. Su, H. Yu, C.Y. Cheng, et al., Inhibition of the STAT3 signaling pathway contributes to apigenin-mediated anti-metastatic effect in melanoma, Scientific reports 6 (2016) 21731.
[132] M. Piantelli, C. Rossi, M. Iezzi, R. La Sorda, S. Iacobelli, S. Alberti, et al., Flavonoids inhibit melanoma lung metastasis by impairing tumor cells endothelium interactions, Journal of Cellular Physiology. 207 (1) (2006) 23–29.
[133] J.-H. Yang, J. Hu, L. Wan, L.-J. Chen, Barbigerone inhibits tumor angiogenesis, growth and metastasis in melanoma, Asian Pacific journal of cancer prevention: APJCP. 15 (1) (2014) 167–174.
[134] A.A. Carvalho, P.M. da Costa, Souza LGDS, T.L.G. Lemos, Alves APNN, C. Pessoa, et al., Inhibition of metastatic potential of B16-F10 melanoma cell line in vivo and in vitro by biflorin, Life sciences 93 (5-6) (2013) 201–207.
[135] Y.-W. Lai, S.-W. Wang, C.-H. Chang, S.-C. Liu, Y.-J. Chen, C.-W. Chi, et al., Butein inhibits metastatic behavior in mouse melanoma cells through VEGF expression and translation-dependent signaling pathway regulation, BMC complementary and alternative medicine 15 (1) (2015) 445.
[136] N. Di Leo, M. Battaglini, L. Berger, M. Giannaccini, L. Dente, S. Hampel, et al., A catechin nanoformulation inhibits WM266 melanoma cell proliferation, migration and associated neo-angiogenesis, European Journal of Pharmaceutics and Biopharmaceutics. 114 (2017) 1–10.
[137] C.M. Cabello, I.I.I.W.B. Bair, S.D. Lamore, S. Ley, A.S. Bause, S. Azimian, et al., The cinnamon-derived Michael acceptor cinnamic aldehyde impairs melanoma cell proliferation, invasiveness, and tumor growth, Free Radical Biology and Medicine. 46 (2) (2009) 220–231.
[138] V.P. Murali, G. Kuttan, Curculigoside augments cell-mediated immune responses in metastatic tumor-bearing animals, Immunopharmacology and immunotoxicology 38 (4) (2016) 264–269.
[139] A. Chatterjee, A. Mitra, S. Ray, N. Chattopadhyay, M. Siddiqi, Curcumin exhibits antimetastatic properties by modulating integrin receptors, collagenase activity, and expression of Nm23 and E-cadherin, Journal of Environmental Pathology, Toxicology and Oncology. 22 (1) (2003).
[140] C. Martinez, V. Vicente, J. Yanez, M. Alcaraz, M. Castells, M. Canteras, et al., The effect of the flavonoid diosmin, grape seed extract and red wine on the pulmonary metastatic B16F10 melanoma, Histology and histopathology. 20 (4) (2005) 1121–1130.
[141] N. Alvarez, V. Vicente, C. Martinez, Synergistic effect of diosmin and interferon-α on metastatic pulmonary melanoma, Cancer Biotherapy and Radiopharmaceuticals. 24 (3) (2009) 347–352.
[142] H.C. Pal, R.D. Baxter, K.M. Hunt, J. Agarwal, C.A. Elmets, M. Athar, et al., Fisetin, a phytochemical, potentiates sorafenib-induced apoptosis and abrogates tumor growth in athymic nude mice implanted with BRAF-mutated melanoma cells, Oncotarget. 6 (29) (2015) 28296.
[143] W. Zhang, Y. Lan, Q. Huang, Z. Hua, Galangin induces B16F10 melanoma cell apoptosis via mitochondrial pathway and sustained activation of p38 MAPK, Cytotechnology. 65 (3) (2013) 447–455.
[144] H. Shi, Y. Wu, Y. Wang, M. Zhou, S. Yan, Z. Chen, et al., Liquiritigenin potentiates the inhibitory effects of cisplatin on invasion and metastasis via downregulation MMP-2/9 and PI3 K/AKT signaling pathway in B16F10 melanoma cells and mice model, Nutrition and cancer 67 (5) (2015) 761–770.
[145] K. Ikeda, Y. Sakai, H. Nagase, Inhibitory effect of magnolol on tumour metastasis in mice, Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 17 (8) (2003) 933–937.
[146] A. Lentini, C. Forni, B. Provenzano, S. Beninati, Enhancement of transglutaminase activity and polyamine depletion in B16-F10 melanoma cells by flavonoids naringenin and hesperitin correlate to reduction of the in vivo metastatic potential, Amino acids 32 (1) (2007) 95–100.
[147] P. Ferrer, M. Asensi, R. Segarra, A. Ortega, M. Benlloch, E. Obrador, et al., Association between pterostilbene and quercetin inhibits metastatic activity of B16 melanoma, Neoplasia. 7 (1) (2005) 37–47.
[148] H.-H. Cao, Tse AK-W, H.-Y. Kwan, H. Yu, C.-Y. Cheng, T. Su, et al., Quercetin

exerts anti-melanoma activities and inhibits STAT3 signaling, Biochemical pharmacology 87 (3) (2014) 424–434.
[149] H.H. Cao, C.Y. Cheng, T. Su, X.Q. Fu, H. Guo, T. Li, et al., Quercetin inhibits HGF/c-Met signaling and HGFstimulated melanoma cell migration and invasion, Molecular Cancer. 14 (1) (2015).
[150] C. Salado, E. Olaso, N. Gallot, M. Valcarcel, E. Egilegor, L. Mendoza, et al., Resveratrol prevents inflammation-dependent hepatic melanoma metastasis by inhibiting the secretion and effects of interleukin-18, Journal of translational medicine. 9 (1) (2011) 59.
[151] S. Bhattacharya, S.R. Darjatmoko, A.S. Polans, Resveratrol modulates the malignant properties of cutaneous melanoma via changes in the activation and attenuation of the anti-apoptotic proto-oncogenic protein Akt/PKB, Melanoma research 21 (3) (2011) 180.
[152] C. Martínez Conesa, V. Vicente Ortega, M.J. Yáñez Gascón, M. Alcaraz Baños, M. Canteras Jordana, O. Benavente-García, et al., Treatment of metastatic melanoma B16F10 by the flavonoids tangeretin, rutin, and diosmin, Journal of agricultural and food chemistry. 53 (17) (2005) 6791–6797.
[153] K. Zhao, X. Song, Y. Huang, J. Yao, M. Zhou, Z. Li, et al., Wogonin inhibits LPS-induced tumor angiogenesis via suppressing PI3K/Akt/NF-κB signaling, European journal of pharmacology 737 (2014) 57–69.