Review Article

Emerging Perspective: Role of Increased ROS and Redox Imbalance in Skin Carcinogenesis

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Strategies to battle malignant tumors have always been a dynamic research endeavor. Although various vehicles (e.g., chemotherapeutic therapy, radiotherapy, surgical resection, etc.) are used for skin cancer management, they mostly remain unsatisfactory due to the complex mechanism of carcinogenesis. Increasing evidence indicates that redox imbalance and aberrant reactive oxygen species (ROS) are closely implicated in the oncogenesis of skin cancer. When ROS production goes beyond their clearance, excessive or accumulated ROS could disrupt redox balance, induce oxidative stress, and activate the altered ROS signals. These would damage cellular DNA, proteins, and lipids, further leading to gene mutation, cell hyperproliferation, and fatal lesions in cells that contribute to carcinogenesis in the skin. It has been known that ROS-mediated skin carcinogenesis involves multiple ways, including modulating related signaling pathways, changing cell metabolism, and causing the instability of the genome and epigenome. Nevertheless, the exact role of ROS in skin cancer has not been thoroughly elucidated. In spite of ROS inducing skin carcinogenesis, toxic-dose ROS could trigger cell death/apoptosis and, therefore, may be an efficient therapeutic tool to battle skin cancer. Considering the dual role of ROS in the carcinogenesis and treatment of skin cancer, it would be essential to clarify the relationship between ROS and skin cancer. Thus, in this review, we get the related data together to seek the connection between ROS and skin carcinogenesis. Besides, strategies basing on ROS to fight skin cancer are discussed.

1. Introduction

Skin cancer is the most common type of cancer, and its incidence has gradually increased in recent years [1]. It is characterized by aberrant cell growth with a potential to invade or spread elsewhere in the body, which involves the complex process of carcinogenesis [2]. At present, the main types of skin cancer are melanoma and nonmelanoma skin cancer (NMSC), while the latter includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Ultraviolet (UV) exposure is one of the main factors inducing skin cancer, and cutaneous cells may be damaged directly by UV radiation or indirectly by UV-mediated reactive oxygen species (ROS) overproduction [3]. Long-term UV radiation could cause photochemical reactions or/and oxidative DNA damage, induce DNA mutation and misexpression, and trigger skin carcinogenesis [4]. UV irradiation induces the skin to produce substantial ROS, which results in nuclear DNA damage via forming a large amount of cyclobutane pyrimidine dimers (CPDs), pyrimidine (6-4), pyrimidone photoproducts, and 8-oxodG [5]. 8-oxodG, a biomarker of oxidative damage to DNA, could be removed from the damaged DNA by the enzyme human 8-oxoguanine-DNA glycosylase 1 (hOGG1). In the study, it was shown that UVB-induced ROS triggered 8-oxoguanine (8-oxoG) production and hOGG1 reduction in the skin, further damaging the DNA repair pathway, and eventually initiating cutaneous carcinogenesis [6, 7].

ROS belong to oxygen-derived small molecules including oxygen-centered radical species (e.g., superoxide (O$_2^-$)), hydroxyl (·OH), peroxyl (R-O$_2^-$), and alkoxyl (RO·) and nonradical compounds that are either oxidizing agents or...
2. Role of ROS in Carcinogenesis

There are two ways for ROS to work in carcinogenesis: genotoxicity and nongenotoxicity. The former is chiefly about genotoxic substance-induced direct DNA damage, which may cause protooncogene activation, tumor suppressor gene inactivation, genomic instability, and epigenetic modifications, further leading to mutations. The latter has an indirect effect on DNA through the activation of related signaling pathways. The following are the details that ROS mediate in cancer, skin cancer in particular, through these two ways.

2.1. ROS-Mediated Genotoxicity in Carcinogenesis

2.1.1. Genomic Instability. As one of the most potent DNA-damaging agents, ROS induce genomic instability in numerous ways. ROS, derived from mitochondrial respiratory chain complex III, greatly encourage DNA oxidative damage, not only destroying DNA bases to generate 7,8-dihydro-8-oxo-2'-deoxyguanosine (8-oxodG) but also producing spontaneous DNA double-strand breaks (DSBss), ultimately resulting in chromosomal aberrations and the accumulation of tyrosine kinase inhibitor-resistant BCR-ABL1 mutants [22]. Weyemi et al. in their reports showed that ROS-produced NOX4 played a critical role in oncogenic Ras-induced DNA damage. H-Ras continuously stimulated the overexpression of NOX4 and its functional partner p22phox, and thereby produced a large amount of H₂O₂ which would over, treatments based on ROS for skin cancer, including chemotherapy, phototherapy, radiotherapy, and dietary antioxidants, are also discussed.

2.1.2. Epigenetic Changes. On the other hand, ROS-induced epigenetic instability/modification also plays an important part in carcinogenesis via the genotoxicity way. The ROS-induced epigenetic modification often manifests as a global hypomethylation of the genome and an abnormal
hypermethylation in the CpG island region of some genes. ROS could promote DNA methylation to result in the silence of the tumor suppressor gene and the activation of oncogene by upregulating the expression of DNA methyltransferases (DNMTs) or by forming a new DNMT-containing complex [32]. For example, H₂O₂ powerfully induced the hypermethylation of CDX1 or runt domain transcription factor 3 (RUNX3) promoter and silenced these genes in colorectal cancer, which indicated that ROS could promote cancer cell proliferation by inducing tumor inhibitor gene silence [33, 34]. As the main scavenger of ROS, glutathione peroxidase 3 (GPX3) is considered to be a potent tumor suppressor in many cancers; nevertheless, GPX3 promoter hypermethylation could stop its antioxidant function in clear cell renal cell carcinoma (ccRCC), which indicates that the failure of the antioxidant system in ccRCC cells may be related to renal carcinogenesis [35]. Furthermore, ROS could promote carcinogenesis through mediating histone modifications or interfering microRNA (miRNA) dysregulation. Gene activation or inhibition caused by ROS-mediated histone modification depends on the modified amino acid residues, and histone acetylation modification is mainly coordinated by histone acetyltransferase (HAT) and histone deacetylase (HDAC), while the level of histone acetylation is always low in cancer cells; especially, the hypomethylation of histone H3K9 leads to melanoma epigenetic instability [36]. Besides, ROS-induced miRNA (such as miR-125b) dysregulation is closely implicated in skin carcinogenesis via interfering with the normal activities of key genes [37].

2.2. ROS-Mediated Nongenotoxicity in Carcinogenesis: Abnormal Activation of Cellular Signaling Pathways. Moderate-dose ROS like O₂⁻ and H₂O₂ facilitate the abnormal proliferation, metastasis, and infiltration of various tumor cells through activating multiple pathways including oxidative stress-related pathways and antioxidant stress pathways, such as the mitogen activated-protein kinase (MAPK) pathway, the phosphoinositide-3-kinase (PI3K)/protein kinase B (PKB or AKT)/mammalian target of rapamycin (mTOR) pathway, the nuclear factor-κB (NF-κB) pathway, and the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway [38]. First, the MAPK signal pathway, consisting of the extracellular-regulated kinase (ERK), the c-Jun N-terminal kinase (JNK), and the p38 kinase isoenzyme, effectively works in mitosis, metabolism, cell proliferation, and growth [39]. In many studies, it has been observed that elevated ROS could activate the MAPK/ERK signaling pathway and enhance the proliferation, invasion, and metastasis of tumor cells [40, 41]; most melanoma patients carried BRAF gene mutations, which might activate the MAPK/ERK signaling pathway, further promoting tumor cell proliferation through regulating the downstream signals, and ultimately leading to tumorigenesis and even tumor progression [42]. Second, the PI3K/AKT/mTOR pathway, as a classic signaling pathway, widely exists in cells to promote cell survival, inhibit apoptosis, and prevent autophagy; this pathway is overactivated in various tumor tissues and facilitates carcinogenesis and angiogenesis [43, 44]. ROS are able to activate the PI3K/AKT/mTOR pathway and mediate the
proliferation and migration of tumor cells [45]. Indeed, ROS enhance the proliferation of melanoma cells via stimulating the PI3K/AKT pathway that interacts with the MAPK pathway [46]. Third, the NF-κB signaling pathway is greatly activated by increased ROS in cancer cells and has a large influence on carcinogenesis [47]. Accumulating findings indicate that NF-κB target genes remarkably benefit cellular survival. It has been shown that ROS could activate the NF-κB signal pathway to promote the angiogenesis and progression of melanoma [48, 49]. On the contrary, the metastatic activity of malignant cells would significantly decrease when ROS-mediated NF-κB activation was suppressed [50]. Fourth, Nrf2 has a dual effect of antitumorigenesis and pro-tumorigenesis in different stages [51]. In the early stage of UV-induced skin carcinogenesis, Nrf2 activation promotes the proliferation of normal cells which greatly outnumbers precancerous cells, and prevents precancerous cell expansion and mutant transformation. Inversely in the late stage, Nrf2 activation is quite beneficial to precancerous/cancerous cell survival, due to oncogene mutations providing higher proliferation and viability for these cells via upregulating Nrf2 expression [52]. On one hand, Nrf2 facilitates carcinogenesis and cancer cell growth/proliferation; numerous studies have demonstrated that Nrf2 highly expresses in a variety of cancer cells and promotes ROS detoxification and tumorigenesis [53–55]. Meanwhile, ROS-related Nrf2 activation of macrophages increased vascular endothelial growth factor (VEGF) expression and facilitated cancer cell EMT [56]. Another study showed that the activated Nrf2 positively worked in skin tumor by protecting the protumorigenic activity of keratinocytes from ROS-induced damage and apoptosis [57]. On the other hand, Nrf2 has an antitumorigenesis effect. The decreased Nrf2 spoils the impaired antioxidant defense system, which may increase the incidence of skin cancer including melanoma, SCC, and BCC [58]. Similarly, Nrf2 knockout mice were more susceptible to SCC than controls [59]. More importantly, it has been demonstrated that Nrf2 knockout mice could be subjected to persistent DNA damage, substantial extracellular matrix degradation, and serious inflammation; inversely, the activation of Nrf2 benefited the prevention of skin carcinogenesis in Nrf2 knockout mice [60]. Therefore, the activation of Nrf2 would be a promising strategy for the treatment and prevention of skin carcinogenesis by improving antioxidant capacity to protect cells from oxidative damage. Many Nrf2-activating compounds are beneficial to the prevention of skin cancer, and they contain curcumin, quercetin, and resveratrol [61]. Besides, other redox signaling pathways are implicated in carcinogenesis and tumor development, containing Wnt/β-catenin, TGF-β/Smad, etc. [62, 63]. Figure 2 sketches the role of ROS in carcinogenesis, especially in skin carcinogenesis.

3. Relationship between ROS and Skin Cancer

ROS could promote cutaneous carcinogenesis and cancer progression by mediating related pathways. But until now, the mechanism of ROS influencing skin cancer has not been completely clarified and only part of them have been explored. Herein, we endeavour to elucidate the relationship between ROS and skin cancer basing on the related data.
Melanoma, derived from melanocytes, is a highly invasive tumor with the incidence increasing yearly [64]. Excessive UV exposure is a crucial susceptibility factor, and UV-produced substantial ROS contribute to nuclear DNA damage. ROS not only trigger the occurrence and development of melanoma by way of genotoxicity and some specific signaling pathway activation but they also cause oncogene activation or tumor-suppressing gene inactivation in melanoma consisting of BRAF, c-Myc, p53, and Ras genes. N-Ras is upstream of the MAPK pathway, and its mutation commonly occurs in melanoma, which contributes to cancer cell proliferation [65]. Moreover, ROS also drive the stable expression of HIF-1α to activate the Met protooncogene, which facilitates the proliferation of the extracellular matrix, angiogenesis, and the proliferation and metastasis of melanoma cells [66]. Other oncogenes, RAC1 in particular, are associated with an increased risk of melanoma [67]. The activation of RAC1 depends on the levels of ROS and determines the ability of the migration and invasion of B16 melanoma cells which could be weakened by the suppression of ROS-mediated Rac-1 activation [68]. Apart from the above-mentioned factors, other signaling pathways especially the PI3K/AKT pathway and NF-κB are implicated in the initiation and progression of melanoma [69]. Therefore, ROS are crucially responsible for the occurrence and development of melanoma through inducing related gene mutations and activating a serial of signaling pathways [70]. However, too much ROS generation would encourage apoptosis, which may become a useful vehicle to kill melanoma cells. Subsequently, these will be discussed in the follow-up part of treatments.

Originating from the basal cells near the epidermis-dermis junction, BCC primarily occurs in middle-aged and elderly people, and its lesions mostly appear in exposed areas such as the head, face, and neck. Many factors (e.g., UV, some harmful chemicals, and IR) may trigger BCC initiation, among which UV exposure is a particularly important one [71]. UV-induced ROS could promote the occurrence and development of BCC by generating 8-oxoG and reducing hOGG1 [6]. The imbalance of ROS would encourage skin inflammation, abnormal metabolism, and decreased immunity, which eventually leads to cell mutation and carcinogenesis. Compared with control individuals, there was a high level of MDA in BCC patients, with a reduction of antioxidant components, which enhanced the occurrence of BCC [72]. In the same way, the expression of oxidative DNA damage product 8-oxoG increased, while the levels of antioxidant enzymes may enhance toxic-dose ROS production and weaken the body’s antioxidant defense, eventually inducing cancer cell death. Thus, more and more ROS-targeted therapies/drugs have been discovered in recent years.

Related researches have shown that celecoxib combined with 5-fluorouracil (5-FU) could suppress the phosphorylation of AKT to reduce the proliferation of SCC cells via producing a large amount of ROS in a dose-dependent manner.

4. Treatments for Skin Cancer Targeting ROS

There are many therapies for skin cancer, including surgery, chemotherapy, radiotherapy, photodynamic therapy (PDT), and molecular targeting therapy, etc., among which surgery is the most common and important one [82]. Nevertheless, numerous studies have shown that higher-level ROS and redox imbalance often emerge from cancer cells, which could cause multidrug resistance (MDR) and immunosuppression of cancer cells and thereby make it quite difficult to control tumors [83]. At the same time, when the skin cancer occurs at a special site, or the lesions are too large or many to operate, or the patient is too old to tolerate surgery, or distant metastasis of tumors occurs, other medical approaches such as radiotherapy, PDT, and/or chemotherapy may be better alternatives [84]. Given that ROS play an important role in promoting skin cancer, many ROS-targeted treatments would be well developed (shown in Figure 3).

4.1. Medical Treatments for Skin Cancer Basing on ROS

Skin cancer cells have a higher oxidative environment, and ROS have a double effect on cutaneous carcinoma. On the one hand, reducing ROS production contributes to inhibiting skin cancer; but on the other hand, diminishing antioxidant enzymes may enhance toxic-dose ROS production and weaken the body’s antioxidant defense, eventually inducing cancer cell death. Thus, more and more ROS-targeted therapies/drugs have been discovered in recent years.

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Once FU is converted into FU deoxynucleotides in cells, it would block thymidine nucleotide synthetase and inhibit DNA synthesis. FU meanwhile interferes with the synthesis of RNA to resist tumors. Moreover, increased ROS cause oxidative damage and then result in the breakage of NMSC cell membrane lipids, proteins, and DNA strand chain [85, 86]. The targeted inhibitors dabrafenib and trametinib were used to treat melanoma and SCC mainly by involving ROS overproduction and caspase-activated apoptosis [87]. Daniel et al. also found that the combined therapy of vemurafenib and potassium channel inhibitor TRAM-34 decreased ERK phosphorylation and significantly increased intracellular ROS levels, which stimulated caspase-3 and other proapoptotic pathways and decreased the mitochondrial membrane potential, further leading to the apoptosis of melanoma cells [88]. For example, targeting BRAF gene drugs vemurafenib and dabrafenib could inhibit the growth and division of BRAF-mutated metastatic melanoma cells via blocking the MAPK signaling pathway and upregulating ROS [89]. Meanwhile, the MEK inhibitor trametinib combining with dabrafenib significantly enhanced the therapeutic effect on melanoma in the presence of high-level ROS [90]. Besides, chaetocin derived from the Chaetomium species has a powerful antitumor proliferative activity. It significantly inhibited melanoma cell proliferation and promoted its apoptosis via increasing cellular ROS, decreasing the mitochondrial membrane potential and activating the caspase-9/3 pathway [91]. Nevertheless, Yu et al. and Wang et al. discovered that the ROS-responsive gel scaffold that they created in their study could break immune tolerance and enhance immune response to melanoma through reducing the level of local ROS and inhibiting the programmed death-ligand 1 (PD-L1) [92, 93].

PDT is a phototherapy based on the accumulation of photosensitizers in the body and the irradiation of light with a specific wave length, which can generate substantial ROS to produce cytotoxicity and kill cancer cells. Currently, 5-methylaminolevulinic acid (MAL) and 5-aminolevulinic acid (ALA) are both extremely common photosensitizers in PDT, and PDT has been widely used to treat skin tumors, e.g., SCC, BCC, and Bowen’s disease. The presence of either MAL or ALA in the body may be converted into protoporphyrin IX (PpIX) with strong photosensitivity, which produces substantial ROS to kill cancer cells after irradiation with adequate-wavelength light, while neighbouring normal cells are scarcely affected [94]. However, PDT has a large limitation in skin cancer due to the infiltration of photosensitizers into deep skin tissue. To overcome this deficiency, some improvements, including pretreatment with a laser or a microneedle and encapsulating the photosensitizer in nanoparticles and combining with drugs, are made to enhance PDT efficacy in skin cancer [95]. Others, like indoline-fused-triazole-mediated PDT can increase ROS production and enhance apoptosis-related protein expression, thereby inducing BBC cell death [96].

Furthermore, there are other ways for skin cancer treatment targeting ROS. Typically, radiotherapy is an effective vehicle in the management of skin cancer in recent decades [97]. Via locally producing and releasing a large quantity of ROS, radiotherapy can cause violent oxidative eruptions to kill tumor cells and make solid tumor smaller [98]. Recently, it has been demonstrated that some ROS-inducers are conducive to enhancing the sensitivity of skin cancer cells to IR through a ROS-mediated manner. Selenadiazole derivatives, for example, could increase the sensitivity of A375 human melanoma cells to X-ray by the induction of ROS-mediated DNA damage and AKT inactivation. Besides, IR benefits more ROS generation, G2/M phase arrest, and melanoma cell apoptosis [99].
4.2. Dietary Antioxidants for Skin Cancer Basing on ROS.
Dietary antioxidants are widely distributed in fruits, vegetables, grain, herbs, spices, and other foods, which are rich in vitamins, minerals, polyphenols, and flavonoids. Dietary antioxidants possess various antineoplastic activities: anti-proliferation, anti-inflammation, immune regulation, antiangiogenesis, and inhibition of metastasis [100, 101]. Dietary intake of vitamins, including vitamin C, vitamin E, selenium, and vitamin A, is inversely proportional to the risk of cancer and prevents skin carcinogenesis as antioxidant micronutrients [102]. When UV-induced ROS are beyond the antioxidant defense, oxidative stress occurs; nevertheless, these vitamins could effectively eliminate ROS and prevent oxidative stress through strengthening the antioxidant defense, ultimately protecting the skin against UV-induced cancer [103]. Moreover, polyphenols are a group of natural substances with excellent biological properties and have become potent dietary-preventive agents against cancer. The polypodium leucotomos extract (PL), a strong antioxidant with high-content phenolic compound, is able to prevent and control skin cancer mainly by inhibiting UV-induced ROS production, suppressing NF-κB activation, and activating the p53 protein [104]. Heo et al. found that the decrease of Nrf2 expression and the antioxidant defense ability in resveratrol-treated melanoma cells encouraged the generation of a large amount of ROS and endoplasmic reticulum stress, then triggered the occurrence of oxidative stress; in turn, the increased ROS and oxidative stress further inhibited the growth and proliferation of melanoma cells by downregulating the Bcl-2 protein level and upregulating the Bcl-2-related X protein expression [105]. As a member of the flavonoid family, quercetin is excellent in strengthening the antioxidant defense via removing H2O2, O2•−, and “OH and has a powerful anticancer effect on skin cancer through regulating molecular mechanisms, e.g., inhibiting activation of the MAPK, PI3K-Akt/PKB, and NF-κB signal pathways [106]. Another natural flavonoid, caffeic acid n-butyl ester (CAE), stimulates the accumulation of toxic ROS and the decrease of MMP in A431 skin cancer cells to inhibit the PI3K/AKT/mTOR signaling pathway and thus induce cancer cell apoptosis [107]. Lee et al. meanwhile showed that the flavonoid Cudraflavone C was a novel natural drug for the treatment of melanoma; this drug could activate the phosphorylation of MAPKs (p38, ERK, and JNK) and increase the expression of apoptosis proteins (Bax, cytochrome c, caspase-9, and caspase-3/7) to induce the apoptosis of melanoma cells by increasing mitochondrial ROS production [108]. Proanthocyanidins, a group of flavonoids derived from grapes, apples, bilberry, cranberry, and other plants, have potent abilities of deducing the proliferation and invasion of tumor cells through the production of toxic-dose ROS and inhibition of MMP-2/9 expression, eventually preventing skin carcinogenesis, especially SCC [109]. Other studies also have demonstrated that proanthocyanidins, owing to their strong antineoplastic and antiangiogenic properties in cancers, could downregulate VEGF expression, suppress endothelial cell migration, and lessen vascularization via attenuating the phosphorylation of Akt, ERK, and p38 MAPK [110]. In addition, dietary antioxidants like some Thai plants have protective effects against UV-induced skin cancer [111]. Overall, dietary antioxidants have diverse beneficial properties and provide a protection against skin cancer through regulating some molecular mechanisms between ROS and cancer.

Figure 3 summarizes these ROS-targeted treatments on skin cancer.

5. Conclusion and Future Perspective
Taken together, there is convincing evidence to support the critical role of ROS in cutaneous carcinogenesis and skin cancer progression. Increased ROS contribute to DNA damage and epigenetic instability, metabolic adaptation, cancer cell proliferation and migration, and cell death in some cases. In recent years, it has become a research hot spot in the tumor therapy field whether to focus on antioxidation or promote oxidation. In this review, a series of mechanisms in ROS-mediated skin cancers have been discussed, including protooncogene activation, tumor suppressor gene inactivation, genomic instability/mutations, and epigenetic modifications, as well as multiple related signaling pathways; several therapeutic approaches targeting ROS, like PDT, radiotherapy, and dietary therapy, are also introduced. Although the relationship between ROS and skin carcinogenesis has been largely elucidated, how they specifically regulate each other needs further research. We look forward to finding the balance between ROS and skin carcinogenesis in the near future and searching a reliable and effective method for the treatment of skin cancer.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Authors’ Contributions
Dehai Xian and Rui Lai are coauthors.

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References
[1] M. Hosseini, Z. Kasraian, and H. R. Rezvani, “Energy metabolism in skin cancers: a therapeutic perspective,” Biochimica et Biophysica Acta - Bioenergetics, vol. 1858, no. 8, pp. 712–722, 2017.
[2] P. S. Roy and B. J. Saikia, “Cancer and cure: a critical analysis,” Indian Journal of Cancer, vol. 53, no. 3, pp. 441-442, 2016.
[3] F. Liu-Smith, J. Jia, and Y. Zheng, “UV-induced molecular signaling differences in melanoma and non-melanoma skin cancer,” Advances in Experimental Medicine and Biology, vol. 996, pp. 27–40, 2017.
[4] A. Kyrgidis, T. G. Tzellos, K. Vahtsevanos, and S. Triaridis, “New concepts for basal cell carcinoma. Demographic, clinical, histological risk factors, and biomarkers. A systematic
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[5] G. P. Pfeifer and A. Besaratinia, "UV wavelength-dependent DNA damage and human non-melanoma and melanoma skin cancer," *Photochemical & Photobiological Sciences*, vol. 11, no. 1, pp. 90–97, 2012.

[6] X. X. Huang, R. A. Scloyer, A. Abubakar, and G. M. Halliday, "Human 8-oxoguanine-DNA glycosylase-1 is downregulated in human basal cell carcinoma," *Molecular Genetics and Metabolism*, vol. 106, no. 1, pp. 127–130, 2012.

[7] M. Kunisada, F. Yogianti, K. Sakumi, R. Ono, Y. Nakabeppu, and C. Nishigori, "Increased expression of versican in the inflammatory response to UBV and reactive oxygen species-induced skin tumorigenesis," *The American Journal of Pathology*, vol. 179, no. 6, pp. 3056–3065, 2011.

[8] J. N. Moloney and T. G. Cotter, "ROS signalling in the biology of cancer," *Seminars in Cell & Developmental Biology*, vol. 80, pp. 50–64, 2018.

[9] S. I. Liochev, "Reactive oxygen species and the free radical theory of aging," *Free Radical Biology & Medicine*, vol. 60, pp. 1–4, 2013.

[10] L. A. Sena and N. S. Chandel, "Physiological roles of mitochondrial reactive oxygen species," *Molecular Cell*, vol. 48, no. 2, pp. 158–167, 2012.

[11] S. Di Meo, T. T. Reed, P. Venditti, and V. M. Victor, "Role of ROS and RNS sources in physiological and pathological conditions," *Oxidative Medicine and Cellular Longevity*, vol. 2016, Article ID 1245049, 44 pages, 2016.

[12] F. Ursini, M. Maiorino, and H. J. Forman, "Redox homeostasis: the golden mean of healthy living," *Redox Biology*, vol. 8, pp. 205–215, 2016.

[13] M. Vucetić, Y. Cormerais, S. K. Parks, and J. Pouysségur, "The central role of amino acids in cancer redox homeostasis: vulnerability points of the cancer redox code," *Frontiers in Oncology*, vol. 7, p. 319, 2017.

[14] M. del Pilar Sosa Idelchik, U. Begley, T. J. Begley, and J. Andrés Meléndez, "Mitochondrial ROS control of cancer," *Seminars in Cancer Biology*, vol. 27, pp. 57–66, 2017.

[15] M. Valiko, K. Jomova, C. J. Rhodes, K. Kuča, and K. Musílek, "Redox and non-redox-metal-induced formation of free radicals and their role in human disease," *Archives of Toxicology*, vol. 90, no. 1, pp. 1–37, 2016.

[16] U. Wößle, G. Seelinger, G. Bauer, M. C. Meinke, J. Lademann, and C. M. Schempp, "Reactive molecule species and antioxidative mechanisms in normal skin and skin aging," *Skin Pharmacology and Physiology*, vol. 27, no. 6, pp. 316–332, 2014.

[17] J. Rudolf, H. Raad, A. Taieb, and H. R. Rezvani, "NADPH oxidases and their roles in skin homeostasis and carcinogenesis," *Antioxidants & Redox Signaling*, vol. 28, no. 13, pp. 1238–1261, 2018.

[18] A. G. Georgakilas, "Oxidative stress, DNA damage and repair in carcinogenesis: have we established a connection?", *Cancer Letters*, vol. 327, no. 1-2, pp. 3–4, 2012.

[19] E. Emanuele, J. M. Spencer, and M. Braun, "From DNA repair to proteome protection: new molecular insights for preventing non-melanoma skin cancers and skin aging," *Journal of Drugs in Dermatology*, vol. 13, no. 3, pp. 274–281, 2014.

[20] J. Kim, J. Kim, and J. S. Bae, "ROS homeostasis and metabolism: a critical liaison for cancer therapy," *Experimental & Molecular Medicine*, vol. 48, no. 11, article e269, 2016.

[21] S. Prasad, S. C. Gupta, and A. K. Tyagi, "Reactive oxygen species (ROS) and cancer: role of antioxidative nutraceuticals," *Cancer Letters*, vol. 387, pp. 95–105, 2017.

[22] M. Nieborowska-Skorska, P. K. Kopinski, R. Ray et al., "Rac2-MRC-cIII-generated ROS cause genomic instability in chronic myeloid leukemia stem cells and primitive progenitors," *Blood*, vol. 119, no. 18, pp. 4253–4263, 2012.

[23] U. Weyemi, O. Lagente-Chevallier, M. Boufraqech et al., "ROS-generating NADPH oxidase NOX4 is a critical mediator in oncogenic H-Ras-induced DNA damage and subsequent senescence," *Oncogene*, vol. 31, no. 9, pp. 1117–1129, 2012.

[24] M.-T. Park, M.-J. Kim, Y. Suh et al., "Novel signaling axis for ROS generation during K-Ras-induced cellular transformation," *Cell Death and Differentiation*, vol. 21, no. 8, pp. 1185–1197, 2014.

[25] F. Liu-Smith, R. Dellinger, and F. L. Meyskens Jr., "Updates of reactive oxygen species in melanoma etiology and progression," *Archives of Biochemistry and Biophysics*, vol. 563, pp. 51–55, 2014.

[26] E. Aydin, J. Johansson, F. H. Nazir, K. Hellstrand, and A. Martner, "Role of NOX2-derived reactive oxygen species in NK cell-mediated control of murine melanoma metastasis," *Cancer Immunology Research*, vol. 5, no. 9, pp. 804–811, 2017.

[27] S. Antony, G. Jiang, Y. Wu et al., "NADPH oxidase 5 (NOX5)—induced reactive oxygen signaling modulates normoxic HIF-1α and p27^Kip1 expression in malignant melanoma and other human tumors," *Molecular Carcinogenesis*, vol. 56, no. 12, pp. 2643–2662, 2017.

[28] M. Li, Q. Chen, and X. Yu, "Chemopreventive effects of ROS targeting in a murine model of BRCA1-deficient breast cancer," *Cancer Research*, vol. 77, no. 2, pp. 448–458, 2017.

[29] A. V. Budanov, "Stress-responsive sestrins link p53 with redox regulation and mammalian target of rapamycin signaling," *Antioxidants & Redox Signaling*, vol. 15, no. 6, pp. 1679–1690, 2011.

[30] F. Mantovani, L. Collavin, and G. Del Sal, "Mutant p53 as a guardian of the cancer cell," *Cell Death and Differentiation*, vol. 26, no. 2, pp. 199–212, 2019.

[31] M. Nakayama and M. Oshima, "Mutant p53 in colon cancer," *Journal of Molecular Cell Biology*, vol. 11, no. 4, pp. 267–276, 2019.

[32] Q. Wu and X. Ni, "ROS-mediated DNA methylation pattern alterations in carcinogenesis," *Current Drug Targets*, vol. 16, no. 1, pp. 13–19, 2015.

[33] R. Zhang, K. A. Kang, K. C. Kim et al., "Oxidative stress causes epigenetic alteration of CDX1 expression in colorectal cancer cells," *Gene*, vol. 524, no. 2, pp. 214–219, 2013.

[34] K. A. Kang, R. Zhang, G. Y. Kim, S. C. Bae, and J. W. Hyun, "Epigenetic changes induced by oxidative stress in colorectal cancer cells: methylation of tumor suppressor RUNX3," *Tumour Biology*, vol. 33, no. 2, pp. 403–412, 2012.

[35] Q. Liu, J. Jin, J. Ying et al., "Frequent epigenetic suppression of tumor suppressor gene glutathione peroxidase 3 by promoter hypermethylation and its clinical implication in clear cell renal cell carcinoma," *International Journal of Molecular Sciences*, vol. 16, no. 12, pp. 10636–10649, 2015.
[36] Y. Sang and Y. Deng, “Current insights into the epigenetic mechanisms of skin cancer,” *Dermatologic Therapy*, vol. 32, no. 4, article e12964, 2019.

[37] J. He and B. H. Jiang, “Interplay between reactive oxygen species and microRNAs in cancer,” *Current Pharmacology Reports*, vol. 2, no. 2, pp. 82–90, 2016.

[38] B. Farhood, M. Najafi, E. Salehi et al., “Disruption of the redox balance with either oxidative or anti-oxidative loading as a promising target for cancer therapy,” *Journal of Cellular Biochemistry*, vol. 120, no. 1, pp. 71–76, 2019.

[39] Y. Sun, W. Z. Liu, T. Liu, X. Feng, N. Yang, and H. F. Zhou, “Signaling pathway of MAPK/ERK in cell proliferation, differentiation, migration, senescence and apoptosis,” *Journal of Receptor and Signal Transduction Research*, vol. 35, no. 6, pp. 600–604, 2015.

[40] C. Wang, P. Li, J. Xuan et al., “Cholesterol enhances colorectal cancer progression via ROS elevation and MAPK signaling pathway activation,” *Cellular Physiology and Biochemistry*, vol. 42, no. 2, pp. 729–742, 2017.

[41] L. Cao, X. Chen, X. Xiao, Q. Ma, and W. Li, “Resveratrol inhibits hyperglycemia-driven ROS-induced invasion and migration of pancreatic cancer cells via suppression of the ERK and p38 MAPK signaling pathways,” *International Journal of Oncology*, vol. 49, no. 2, pp. 735–743, 2016.

[42] G. T. Gibney, J. L. Messina, I. V. Fedorenko, V. K. Sondak, and K. S. M. Smalley, “Paradoxic oncogenesis—the long-term effects of BRAF inhibition in melanoma,” *Nature Reviews Clinical Oncology*, vol. 10, no. 7, pp. 390–399, 2013.

[43] X. Liu, L. Zhang, Y. Liu et al., “Girc-8073 regulates CEP55 by sponging miR-449a to promote caprine endometrial epithelial cells proliferation via the PI3K/AKT/mTOR pathway,” *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*, vol. 1865, no. 8, pp. 1130–1147, 2018.

[44] X. Tan, Z. Zhang, H. Yao, and L. Shen, “Tim-4 promotes the growth of colorectal cancer by activating angiogenesis and recruiting tumor-associated macrophages via the PI3K/AKT/mTOR signaling pathway,” *Cancer Letters*, vol. 436, pp. 119–128, 2018.

[45] A. Silva, A. Girio, I. Cebola, C. I. Santos, F. Antunes, and J. T. Barata, “Intracellular reactive oxygen species are essential for PI3K/Akt/mTOR-dependent IL-7-mediated viability of T-cell acute lymphoblastic leukemia cells,” *Leukemia*, vol. 25, no. 6, pp. 960–967, 2011.

[46] S. Meierjohann, “Oxidative stress in melanocyte senescence and melanoma transformation,” *European Journal of Cell Biology*, vol. 93, no. 1-2, pp. 36–41, 2014.

[47] M. J. Morgan and Z. G. Liu, “Crosstalk of reactive oxygen species and NF-κB signaling,” *Cell Research*, vol. 21, no. 1, pp. 103–115, 2011.

[48] M. K. Schaafhausen, W. J. Yang, L. Centanin et al., “Tumor angiogenesis is caused by single melanoma cells in a manner dependent on reactive oxygen species and NF-κB,” *Journal of Cell Science*, vol. 126, no. 17, pp. 3862–3872, 2013.

[49] I. M. W. Ruma, E. W. Putranto, E. Kondo et al., “MCAM, as a novel receptor for S100A8/A9, mediates progression of malignant melanoma through prominent activation of NF-κB and ROS formation upon ligand binding,” *Clinical & Experimental Metastasis*, vol. 33, no. 6, pp. 609–627, 2016.

[50] A. Kim, M. Im, N. H. Yim, Y. P. Jung, and J. Y. Ma, “Aqueous extract of Bambusae Caulis in Taeanim inhibits PMA-induced tumor cell invasion and pulmonary metastasis: suppression of NF-κB activation through ROS signaling,” *PLoS One*, vol. 8, no. 10, article 78061, 2013.

[51] H. Satoh, T. Moriguchi, D. Saigusa et al., “NRF2 intensifies host defense systems to prevent lung carcinogenesis, but after tumor initiation accelerates malignant cell growth,” *Cancer Research*, vol. 76, no. 10, pp. 3088–3096, 2016.

[52] H. Ikehata and M. Yamamoto, “Roles of the KEAP1-NRF2 system in mammalian skin exposed to UV radiation,” *Toxicology and Applied Pharmacology*, vol. 360, pp. 69–77, 2018.

[53] G. M. DeNicola, F. A. Karthikeyan, T. H. Humphson et al., “Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis,” *Nature*, vol. 475, no. 7354, pp. 106–109, 2011.

[54] A. Cuadrado, A. I. Rojo, G. Wells et al., “Therapeutic targeting of the NRF2 and KEAP1 partnership in chronic diseases,” *Nature Reviews Drug Discovery*, vol. 18, no. 4, pp. 295–317, 2019.

[55] Y. R. Kim, J. E. Oh, M. S. Kim et al., “Oncogenic NRF2 mutations in squamous cell carcinomas of oesopagus and skin,” *The Journal of Pathology*, vol. 220, no. 4, pp. 446–451, 2010.

[56] R. Feng, Y. Morine, T. Ikemoto et al., “Nrf2 activation drive macrophages polarization and cancer cell epithelial-mesenchymal transition during interaction,” *Cell Communication and Signaling*, vol. 16, no. 1, p. 54, 2018.

[57] F. Rolfs, M. Huber, A. Kuchne et al., “Nrf2 activation promotes keratinocyte survival during early skin carcinogenesis via metabolic alterations,” *Cancer Research*, vol. 75, no. 22, pp. 4817–4829, 2015.

[58] C. Y. Choi, J. Y. Kim, S. Y. Lee et al., “Expression of nuclear factor erythroid 2 protein in malignant cutaneous tumors,” *Archives of Plastic Surgery*, vol. 41, no. 6, pp. 654–660, 2014.

[59] E. V. Knatko, M. Higgins, J. W. Fahey, and A. T. Dinkova-Kostova, “Loss of Nrf2 abrogates the protective effect of Keap1 downregulation in a preclinical model of cutaneous squamous cell carcinoma,” *Scientific Reports*, vol. 6, no. 1, article 25804, 2016.

[60] C. L. Saw, A. Y. Yang, M. T. Huang et al., “Nrf2 null enhances UVB-induced skin inflammation and extracellular matrix damage,” *Cell & Bioscience*, vol. 4, no. 1, p. 39, 2014.

[61] K. S. Chun, J. Kundu, J. K. Kundu, and Y. J. Surh, “Targeting Nrf2-Keap1 signaling for chemoprevention of skin carcinogenesis with bioactive phytochemicals,” *Toxicology Letters*, vol. 229, no. 1, pp. 73–84, 2014.

[62] X. Wang, A. K. Mandal, H. Saito et al., “Arsenic and chromium in drinking water promote tumorigenesis in a mouse colitis-associated colorectal cancer model and the potential mechanism is ROS-mediated Wnt/β-catenin signaling pathway,” *Toxicology and Applied Pharmacology*, vol. 262, no. 1, pp. 11–21, 2012.

[63] A. Vallee and Y. Lecarpentier, “Crosstalk between peroxisome proliferator-activated receptor gamma and the canonical WNT/β-catenin pathway in chronic inflammation and oxidative stress during carcinogenesis,” *Frontiers in Immunology*, vol. 9, p. 745, 2018.

[64] M. Rastrelli, S. Tropea, C. R. Rossi, and M. Aiba, “Melanoma: epidemiology, risk factors, pathogenesis, diagnosis and classification,” *In Vivo*, vol. 28, no. 6, pp. 1005–1011, 2014.

[65] R. W. Jenkins and R. J. Sullivan, “NRAS mutant melanoma: an overview for the clinician for melanoma management,” *Melanoma Management*, vol. 3, no. 1, pp. 47–59, 2016.
Oxidative Medicine and Cellular Longevity

[66] G. Comito, M. Calvani, E. Giannoni et al., “HIF-1α stabilization by mitochondrial ROS promotes Met-dependent invasive growth and vasculogenic mimicry in melanoma cells,” Free Radical Biology & Medicine, vol. 51, no. 4, pp. 893–904, 2011.

[67] T. A. Yuan, V. Yourk, A. Farhat et al., “A case-control study of the genetic variability in reactive oxygen species-metabolizing enzymes in melanoma risk,” International Journal of Molecular Sciences, vol. 19, no. 1, p. 242, 2018.

[68] S. J. Park, Y. T. Kim, and Y. J. Jeon, “Antioxidant dieckol downregulates the Rac1/ROS signaling pathway and inhibits Wiskott-Aldrich syndrome protein (WASP)-family verprolin-homologous protein 2 (WAVE2)-mediated invasive migration of B16 mouse melanoma cells,” Molecules and Cells, vol. 33, no. 4, pp. 363–369, 2012.

[69] Y. L. Shih, H. M. Chou, H. C. Chou et al., “Casticin impairs cell migration and invasion of mouse melanoma B16F10 cells via PI3K/AKT and NF-κB signaling pathways,” Environmenta^l Toxicology, vol. 32, no. 9, pp. 2097–2112, 2017.

[70] S. P. Cannavò, A. Tonacci, L. Bertino, M. Casciaro, F. Borgia, and S. Sangemi, “The role of oxidative stress in the biology of melanoma: a systematic review,” Pathology, Research and Practice, vol. 215, no. 1, pp. 21–28, 2019.

[71] T. R. Correia de Sá, R. Silva, and J. M. Lopes, “Basal cell carcinoma of the skin (part1): epidemiology, pathology and genetic syndromes,” Future Oncology, vol. 11, no. 22, pp. 3011–3021, 2015.

[72] Z. Majidi, M. Djalali, M. H. Javanbakht, M. Fathi, M. Zarei, and K. Foladaz, “Evaluation of the level of zinc and malondialdehyde in basal cell carcinoma,” Iranian Journal of Public Health, vol. 46, no. 8, pp. 1104–1109, 2017.

[73] L. Chaisiriwong, R. Wanitphakdeedecha, P. Sithinhamatsuwan et al., “A case-control study of involvement of oxidative DNA damage and alteration of antioxidant defense system in patients with basal cell carcinoma: modulation by tumor removal,” Oxidative Medicine and Cellular Longevity, vol. 2016, Article ID 5934024, 12 pages, 2016.

[74] C. Pellegrini, M. Maturo, L. di Nardo, V. Ciciarelli, C. Gutiérrez García-Rodrigo, and M. Fargnoli, “Understanding the molecular genetics of basal cell carcinoma,” International Journal of Molecular Sciences, vol. 18, no. 11, p. 2485, 2017.

[75] A. Yoshifuku, K. Fujii, and T. Kanekura, “Comparison of oxidative stress on DNA, protein and lipids in patients with actinic keratosis, Bowen’s disease and squamous cell carcinoma,” The Journal of Dermatology, vol. 45, no. 11, pp. 1319–1323, 2018.

[76] R. M. Brand, P. Wipf, A. Durham, M. W. Epperly, J. S. Greenberger, and L. D. Falo Jr., “Targeting mitochondrial oxidative stress to mitigate UV-induced skin damage,” Frontiers in Pharmacology, vol. 9, p. 920, 2018.

[77] C. L. Benjamin and H. N. Ananthaswamy, “p53 and the pathogenesis of skin cancer,” Toxicology and Applied Pharmacology, vol. 224, no. 3, pp. 241–248, 2007.

[78] R. Kumar, G. Deep, and R. Agarwal, “An overview of ultraviolet B radiation-induced skin cancer chemoprevention by silybin,” Current Pharmacology Reports, vol. 1, no. 3, pp. 206–215, 2015.

[79] L. Liu, H. R. Rezvani, H. B. Back et al., “Inhibition of p38 MAPK signaling augments skin tumorigenesis via NOX2 driven ROS generation,” PLoS One, vol. 9, no. 5, article 97245, 2014.

[80] Y. Kitagishi and S. Matsuda, “Redox regulation of tumor suppressor PTEN in cancer and aging (Review),” International Journal of Molecular Medicine, vol. 31, no. 3, pp. 511–515, 2013.

[81] M. Ming, L. Feng, C. R. Shea et al., “PTEN positively regulates UVB-induced DNA damage repair,” Cancer Research, vol. 71, no. 15, pp. 5287–5295, 2011.

[82] M. C. F. Simões, J. S. Sousa, and A. A. C. C. Pais, “Skin cancer and new treatment perspectives: a review,” Cancer Letters, vol. 357, no. 1, pp. 8–42, 2015.

[83] Q. Cui, J. Q. Wang, Y. G. Assaraf et al., “Modulating ROS to overcome multidrug resistance in cancer,” Drug Resistance Updates, vol. 41, pp. 1–25, 2018.

[84] Y. Rong, L. Zuo, L. Shang, and J. G. Bazan, “Radiotherapy treatment for nonmelanoma skin cancer,” Expert Review of Anticancer Therapy, vol. 15, no. 7, pp. 765–776, 2015.

[85] M. W. Sung, D. Y. Lee, S. W. Park et al., “Celecoxib enhances the inhibitory effect of 5-FU on human squamous cell carcinoma proliferation by ROS production,” The Laryngoscope, vol. 127, no. 4, pp. E117–E123, 2017.

[86] L. Metterle, C. Nelson, and N. Patel, “Intrascleral 5-fluorouracil (FU) as a treatment for nonmelanoma skin cancer (NMSC): a review,” Journal of the American Academy of Dermatology, vol. 74, no. 3, pp. 552–557, 2016.

[87] H. P. Tham, K. Xu, W. Q. Lim et al., “Microneedle-assisted topical delivery of photodynamically active mesoporous formulation for combination therapy of deep-seated melanoma,” ACS Nano, vol. 12, no. 12, pp. 11936–11948, 2018.

[88] D. Bauer, F. Werth, H. A. Nguyen, F. Kiecker, and J. Eberle, “Critical role of reactive oxygen species (ROS) for synergistic enhancement of apoptosis by vemurafenib and the potassium channel inhibitor TRAM-34 in melanoma cells,” Cell Death & Disease, vol. 8, no. 2, article 2594, 2017.

[89] M. Maio, K. Lewis, L. Demidov et al., “Adjuvant vemurafenib in resected, BRAFV600E mutation-positive melanoma: phase 3 study of combination therapy vs. interferon alfa-2b,” The Lancet Oncology, vol. 19, no. 4, pp. 510–520, 2018.

[90] K. K. Broman, L. A. Dossett, J. Sun, Z. Eroglu, and J. S. Zager, “In situ formed reactive oxygen species-responsive scaffold for combination therapy of deep-seated melanoma,” Journal of the American Academy of Dermatology, vol. 67, no. 5, pp. 832–839, 2012.

[91] X. Han, Y. Han, Y. Zheng et al., “Injectable bioreresponsive gel depot for enhanced immune checkpoint blockade,” Advanced Materials, vol. 30, no. 28, article e1801527, 2018.

[92] C. Wang, J. Wang, X. Zhang et al., “In situ production of ROS in the skin by photodynamic therapy as a powerful tool in clinical dermatology,” Methods, vol. 109, pp. 190–202, 2016.
I. Baldea, L. Giurgiu, I. D. Teacoe et al., “Photodynamic therapy in melanoma—where do we stand?”, Current Medicinal Chemistry, vol. 25, no. 40, pp. 5540–5563, 2018.

W. P. Hu, K. K. Kuo, G. C. Senadi, L. S. Chang, and J. J. Wang, “Photodynamic therapy using indolines-fused-iriazoles induces mitochondrial apoptosis in human non-melanoma BCC cells,” Anticancer Research, vol. 37, no. 10, pp. 5499–5505, 2017.

N. Cheraghi, A. Cognetta, and D. Goldberg, “Radiation therapy in dermatology: non-melanoma skin cancer,” Journal of Drugs in Dermatology, vol. 16, no. 5, pp. 464–469, 2017.

Z. Zou, H. Chang, H. Li, and S. Wang, “Induction of reactive oxygen species: an emerging approach for cancer therapy,” Apoptosis, vol. 22, no. 11, pp. 1321–1335, 2017.

Q. Xie, Y. Zhou, G. Lan et al., “Sensitization of cancer cells to radiation by selenadiazole derivatives by regulation of ROS-mediated DNA damage and ERK and AKT pathways,” Biochemical and Biophysical Research Communications, vol. 449, no. 1, pp. 88–93, 2014.

S. Afrin, F. Giampieri, M. Gasparrini et al., “Dietary phytochemicals in colorectal cancer prevention and treatment: a focus on the molecular mechanisms involved,” Biotechnology Advances, 2018.

N. Shapira, “Nutritional approach to sun protection: a suggested complement to external strategies,” Nutrition Reviews, vol. 68, no. 2, pp. 75–86, 2010.

X. Wu, J. Cheng, and X. Wang, “Dietary antioxidants: potential anticancer agents,” Nutrition and Cancer, vol. 69, no. 4, pp. 521–533, 2017.

A. Godic, B. Poljšak, M. Adamic, and R. Dahmane, “The role of antioxidants in skin cancer prevention and treatment,” Oxidative Medicine and Cellular Longevity, vol. 2014, Article ID 860479, 6 pages, 2014.

C. Parrado, M. Mascaraque, Y. Gilaberte, A. Juarranz, and S. Gonzalez, “Fernblock (Polypodium leucotomos extract): molecular mechanisms and pleiotropic effects in light-related skin conditions, photaging and skin cancers, a review,” International Journal of Molecular Sciences, vol. 17, no. 7, p. 1026, 2016.

J. R. Heo, S. M. Kim, K. A. Hwang, J. H. Kang, and K. C. Choi, “Resveratrol induced reactive oxygen species and endoplasmic reticulum stress-mediated apoptosis, and cell cycle arrest in the A375SM malignant melanoma cell line,” International Journal of Molecular Medicine, vol. 42, no. 3, pp. 1427–1435, 2018.

F. Khan, K. Niaz, F. Maqbool et al., “Molecular targets underlying the anticancer effects of quercetin: an update,” Nutrients, vol. 8, no. 9, p. 529, 2016.

N. Zeng, T. Hongbo, Y. Xu, M. Wu, and 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, vol. 17, no. 4, pp. 5652–5657, 2018.

C. W. Lee, F. L. Yen, H. H. Ko et al., “Cudrallavone C induces apoptosis of A375.S2 melanoma cells through mitochondrial ROS production and MAPK activation,” International Journal of Molecular Sciences, vol. 18, no. 7, p. 1508, 2017.

Y. S. Hah, J. G. Kim, H. Y. Cho, J. S. Park, E. P. Heo, and T. J. Yoon, “Proanthocyanidins from Vitis vinifera seeds induce apoptotic and autophagic cell death via generation of reactive oxy-
gen species in squamous cell carcinoma cells,” Oncology Letters, vol. 14, no. 2, pp. 1925–1932, 2017.

Q. Li, X. Wang, T. Dai et al., “Proanthocyanidins, isolated from Choerospondias axillaris fruit peels, exhibit potent antioxidant activities in vitro and a novel anti-angiogenic property in vitro and in vivo,” Journal of Agricultural and Food Chemistry, vol. 64, no. 18, pp. 3546–3556, 2016.

M. B. de Silva and T. Tencomnao, “The protective effect of some Thai plants and their bioactive compounds in UV light-induced skin carcinogenesis,” Journal of Photochemistry and Photobiology. B, vol. 185, pp. 80–89, 2018.