activator proteins, Toll like receptors and interferons [13,14]. Several investigations reported that oxygen mediated free radicals often react with DNA and increase the chance of cancer [15,16]. On top of that, oxidative stress is considered as one of the key regulators in skin carcinogenesis, and thereby identifying nontoxic strong antioxidants to diminish skin cancer is an important area of investigation. Antioxidants strongly prevent both photo-carcinogenesis and skin tumor progression in animal model, in part, by reducing free radicals and reactive oxygen species. These molecules have also been proven highly potent by inhibiting endogenous TNF-α in animal skin, a prime mediator in skin tumor initiator. Furthermore, evidences often suggested that antioxidant inhibit mitogenic and cell survival signaling and initiate apoptosis for cell suppression. Finally, phenolic acid derivatives and flavonoids effectively modulate cell-cycle regulators and check points toward reserve of proliferation, and often arrest growth in G0–G1 phases of a cell cycle [17-19]. Therefore, this study will describe the probable molecular reasons for developing skin cancer along with that a series of therapeutic approaches based on antioxidant molecules will be exposed to prevent skin carcinoma.

Skin Cancer

Cancer, one of the most complicated system in a biological subject which deals with several factors such as alteration of DNA bases, mutation in genetic materials, mutation or blocking of tumor suppressive gene p53 [20,21]. As a result, normal cell of the body lost their control and start replicating their progenitor cells for an enormous numbers which finally act as immortal cells [22]. Every cell has some predetermined functions and they remain in one place for their own survival and biological importance but in cancer, these cells have the ability to travel or spread toward other organs and take control over there. These cells then become malignant tumor and may be threat for a subject [23]. In today's world, men are more prone to prostate cancer, and women are mostly vulnerable towards breast and ovarian cancers but it is skin cancer which affects both the genders [24]. Merkel cell carcinoma, Kaposi sarcoma, Cutaneous (skin) lymphoma, Skin adnexal tumors and different types of sarcomas are rarely observed on skin [25,26]. The most common reason for skin cancer is either sunburn or excess UV exposure, however, family history also plays a major role [27]. Several reports have been suggested where excess UV can cause skin carcinoma in the laboratory animals [28,29]. So far UVA, UVB and UVC have been investigated where UVA and UVB found to have mostly responsible for skin carcinoma, on the contrary, UVC can't reach to the earth due to protection of Ozone layer. Extreme Sun light/UV may penetrate to the skin nucleus and alter/damage genetic code which further leads to abnormal cell replication [30,31]. Often, the Sun penetrates skin cells deeply that these cells are to be damaged. In the affected areas, chemokines and harmful cytokines are accumulated resulting inflammation that may eventually trigger skin cancers [32]. Environmental toxins like smoking, high oxygen atmosphere, household spills and chemical exposures may contain several free radicals and once they enter inside a biological subject, they produce ionization radiation [33]. Inside the body, once ionizing radiation hits a molecule in any cell, an electron may be replaced which ultimately lead to the formation of a highly reactive free radical. The generation of unwanted high levels of free radicals is the mechanism by which ionizing radiation alter necessary proteins, genetic codes and leads to the necrosis of a cell [34]. Skin has been a major target of oxidative stress due to highly reactive free radicals that originate in the environment and in the skin itself that further is responsible for the development of skin carcinoma [35].

Limitations of Chemotherapies

The prevalence of cancer in USA and other western countries is very high and often found tumor who lead normal life [36]. At the initial stage of the tumor progression the treatment on any cancer is easier and to some extend very much curable, however once it reaches towards the metastasis it become more complex and it most cases the treatment seems to be more resistant and the chances of cure become very narrow. Currently, three types of treatment protocol are now being used in the clinic to treat cancer. Radiation which kills individual cells, full or partial removal of tumor cells by surgery and chemotherapies which work against particular cells [37]. In contrast, the treatment of cancer is becoming very difficult owing to following different patterns by the tumor cell. Tumor cells are very distinct and always vary within individuals [38,39]. In addition, it is really difficult to deal with cancer subjects because cancer is a constellation of at least 200 other diseases and it has been often reported that cancer cells are not homogenize [24]. It is always suggested that cancer therapies should optimize most tumor cells and it must be monitored for minimal effect to the normal cells [40]. Unfortunately, all cancer therapies produce severe side effects, adverse effects and are very costly. In majority if the cases, single drug therapy is not sufficient to treat carcinoma. Multiple therapies with several cycles are necessary to optimize the cancer cells. Alopecia, bone marrow depression, severe vomiting, fatigue, rash and heart failure are associated with chemotherapies [41,42]. Most of the anti-tumor drugs are not well studied and many of these are not approved by FDA. Anti-cancer molecules are often contraindicated during pregnancy and several studies suggested that these drugs may interact with foetus and may cause death [43,44]. Besides, several deaths have been reported while given chemotherapies on many clinical evaluations [45,46]. Hepatic and kidney failure have been documented when platinum based chemotherapy was provided [47,48]. Cardiac arrest or arrhythmia have been documented when monoclonal antibodies were administrated to the cancer subjects and sometimes the subjects must be admitted in ICU during prior treatment which increase overall cost [49-51].

An Overview of Antioxidants

Oxidative stress mostly found to be free radical-mediated which further correlates with the response of cellular metabolism and catabolism [52]. In addition, free radicals are mainly generated from mitochondria during ATP production and cellular response in a biological subject. Sometimes drug molecules produce free radicals when given in higher dosage [53]. There are numerous evidences where free radical-mediated oxidative stress linked with many diseases like cardiovascular dysfunctions [54], hepatic damages [55], renal injury [56], diabetes [57], neuro-degeneration [58], aging [59] and other life threatening events [60]. Free radicals are often blamed for acute and chronic inflammation [61] which further drawn with cancers [62,63]. Several approaches against cancer cells have been undertaken targeting reactive oxygen species and often found good results while taken with other synthetic drugs [64]. On the other hand, antioxidants are the molecules which fight against oxidative stress. These are also known as 'free radical scavengers'. Basically, poly-phenols and flavonoids are considered as anti-oxidants which exert several protective mechanisms and found to be effective among *in vivo*, *in vitro* and human subjects [65]. Foods and supplements based

antioxidants have been proved beneficial against free radical mediated damages, at the same time they protect nucleus and necessary enzymes [57,66]. There are multiple studies have been undertaken to investigate anti-cancer activities of antioxidant molecules and some breakthrough outcomes were successfully documented [67,68].

Role of Antioxidant on Skin Cancers

Skin, the biggest organ of the body is protected by several layers. Multiple protective mechanisms have been proposed so far through animal and human studies. Chronic UV exposure-induced skin diseases are mainly caused by the excessive oxidative stress that further leads to inflammation and finally results in DNA and necessary protein damages [35]. DNA protection using antioxidants therapy has been a good choice for clinical trials. Phenolic acid and flavonoids are being reported extremely well against chemoprevention [69]. It is reported that in the TPA-induced skin inflammation model citrus peel extract prevented expression of inducible nitric oxide synthase, cyclooxygenase-2, ornithine decarboxylase, and vascular endothelial growth factor in mouse skin. The study also noticed inhibitory effects of citrus on 7,12-dimethylbenez [a] anthracene (DMBA)/TPA-induced skin tumour formation and reduced tumor incidence, tumor weight and tumor multiplicity of papillomas at 20 weeks treatment [70]. The blocking properties of naringin were observed when in BALB/c mice skin irradiated with UVB. The expressions of interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8) and cyclooxygenase-2 (COX-2) were significantly lowered in Ha CaT cells by primarily blocking MAPK pathways [71]. Src family kinases (SFKs), basically known as oncogenes, are recently drawing attention for their association in melanoma skin cancers; on the other hand, naringin may be an effective molecule for the treatment of melanoma as a natural inhibitor of c-Src [72]. Retinoids such as 13-cis-retinoic acid and retinyl palmitate exhibit a good preventive effect in chemically induced papillomas and carcinomas of the skin in female Swiss mice after three weeks of induction of cancer. The study showed inhibitory effects of retinoids on skin carcinoma [73]. Topical application of vitamin E in a dose-dependent manner has been shown to reduce the incidence of UV-induced skin cancer in mice by exhibiting antioxidant mechanism. Study shows that dimer and trimer products may contribute in avoidance of UV-induced photo-damage in animal [74]. Vitamin C was also found as photo-protectant while applied to mice and pig skin before exposure to ultraviolet radiation (Figure 1) [75,76].

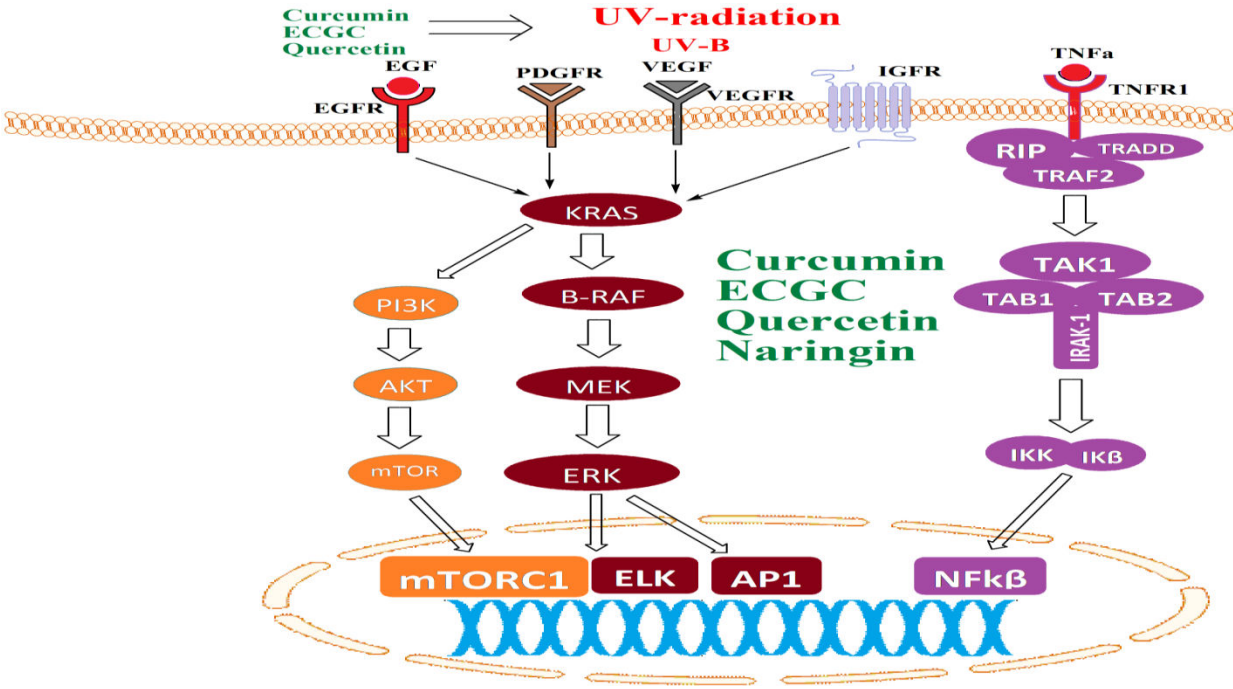

Figure 1: Role of anti-oxidants on skin cancer cell.

A potent antioxidant molecule, Coenzyme Q 10, generally exerts several mechanisms in cancer, inflammation and aging. When Coenzyme Q10 applied on human dermal and epidermal cells, it protects against cell death induced by reactive oxygen species in keratinocytes [77]. A population-based case-control study was performed to investigate the correlation between citrus peel use and black tea intake on squamous cell carcinoma of the skin tissue. Preventive effects of citrus peel and black tea were statistically noticed on human subjects [78]. A study was undertaken with a large number of healthy women whom solar stimulated UV were given on the skin and β-carotene (120 mg) was provided. The study found to be protective by inducing skin lycopene and reducing oxidative markers [79].

The hypothetical pathway explains that there are various extracellular effects can activate the signaling of the growth factor. One of the major reasons of skin cancer is the UV-B from UV radiation. UV-B can influence the mutation of K-RAS which is a upstream signaling kinase of MAPK family. Even though K-RAS signaling is essential for normal cell proliferation and apoptosis but when mutated it is a key player of activating certain signaling pathway that leads to the binding of different transcription factor with DNA that will cause the activation of different cytokines which will participate in the

progression of cancer cell. It has been most commonly known that chronic inflammation leads to the progression of cancer. In skin cancer many studies suggested that activation of TNFR1 by its binding with TNF-α facilitate the synthesis of different inflammatory cytokines. All these factors together participate in the progression of tumor cell. White people are more vulnerable towards the skin cancer than the black and mixed race people. One of the possible reason is the production of melanin is really low in the skin of white people compared to black. However, certain polyphenols and flavons can prevent the mutation from taking place. The underlining reason is yet unknown, due to the lack of study in this particular area it is yet to be discover, but one hypothesis is the hyper activation of the growth factor can be prevented by polyphenols and flavons. They also prevent the phosphorylation of certain kinases, which leads to the apoptosis of those cells. All these activity made them a potential molecule against skin cancer (Table 1).

Subjects	Outcomes of the study	References
Model: Solar simulated irradiation of skin Disease induced by: Radiation Treatment: Ferulic acid Dose: 0.5% Ferulic acid	Caspase 3, 7 density were lowered	[80]
Model: Human keratinocytes Disease induced by: Se methyl selenocysteine Treatment: $Cuso_4$ Dose: N/A	Decreased DNA synthesis, cell growth inhibition, DNA synthesis and Blockade of the cell cycle at the S/G2-M phase and cell death by necrosis.	[81]
Model: CD-1 mice Disease induced by: Genetic Treatment: Lupeol Dose: 1–2 mg/mouse	Decreased protein expression of ODC, cox-2, nitric oxide synthase, and blocked NF-κB and phosphatidyl inositol 3-kinase (PI3K)/Akt signaling in tumor promotion	[82]
Model: Heterozygous DBA/2 MnSOD KO mice Disease induced by: 12-O-tetradecanoylphorbol-13-acetate Treatment: SOD mimetic (MnTE-2-PyP5+) Dose: 5 ng/mouse	suppressed mitosis without interfering with apoptosis, decreased protein carbonyls and reduced the activity of activator protein-1, and prevented the level of proliferating cellular nuclear antigen	[83]
Model: Human Disease induced by: UV light irradiation Treatment: Lutein and zeaxanthin Dose: Lutein 5 mg/zeaxanthin 0.3 mg 2/day	Changed in lipid peroxidation and photo-protective activity in the skin.	[84]
Model: Mouse Disease induced by: Solar ultraviolet (UV) radiation Treatment: (-)-Epigallocatechin-3-gallate (EGCG) Dose: 1 mg/cm^2 skin area	inhibited UVB-induced oxidative stress, significant prevention of UVB-induced depletion of antioxidant enzymes, and Inhibition of a single UVB irradiation-induced phosphorylation of ERK1/2 and MAPK family.	[7]
Model: Skh:2 Hairless Mice Disease induced by: Ultraviolet Irradiation Treatment: Vitamin E Dose: 5% oral and topical RRR-α-tocopheryl acetate	showed no signs of toxicity and had significantly less acute and chronic skin damage induced by UV irradiation, and reduced inflammation and pigmentation.	[29]
Model: Human Disease induced by: Acute UV radiation Treatment: Antioxidant complex – vitamins (lycopene, β-carotene, α-tocopherol), selenium Dose: 3 mg of tomato lycopene, 3 mg of natural α- and b-carotene 5 mg of natural α-tocopherol and 37.5 mg of organic selenium	reduction of the UV-induced erythemas, and Parallel reduction of the lipoperoxide level was observed.	[85]

Model: Mice Disease induced by: UV-induced skin cancer Treatment: Vitamin E and epigallocatechin gallate Dose: Olive oil on the dorsal skin with a moist cotton swab	Delayed the onset of and to reduce the incidence rate of skin cancer development.	[28]
Model: SK-mel28 and A375 human melanoma cells Disease induced by: Genetically induced Treatment: Resveratrol Dose: 30, 60, or 100 mM all-trans-resveratrol	Induced phosphorylation of ERK1/2 in A375	[86]
Model: Healthy women Disease induced by: Solar stimulated light Treatment: β-carotene Dose: 120 mg	Skin lycopene found to be increased and reduced oxidative damages.	[79]
Model: Human Disease induced by: UV light Treatment: Carotenoids and carotenoids plus vitamin E Dose: 25 mg total carotenoids/d and 335 mg (500 IU) RRR-α-tocopherol/d	Dorsal black skin was significantly diminished	[87]
Model: Cell culture Disease induced by: UV or ozone Treatment: Vitamin E Dose: N/A	Combated oxidative stress induced by UV	[88]
Model: Hairless mice Disease induced by: UV exposure Treatment: β-carotene Dose: 10% carotenoids	Reduced skin tumor progression	[89]

Table 1: Role of antioxidant molecules on various cancer induced skin cells.

Conclusion and Future Directions

Evidences suggested that oxidative stress plays a pivotal role in mutation of the different genes, and the expression of many cytokines and chemokines leads to the progression of tumor. It also prevents mitochondrial biogenesis as well, resulting cellular reproduction gets hampered; on the other hand, antioxidants found to be very useful for biogenesis. Although antioxidant molecules have been highly appreciated in the treatment of skin diseases like skin cancers, negative findings are reported too. Both animal and small clinical trials are showing good activities when antioxidant molecules are applied on various skin cancers. Additional larger and wide randomized clinical trials are needed to provide clear scientific reports about the potential benefits of taking antioxidant supplements during skin cancer treatment.

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Conflict of Interest

The authors declare no conflict of interest.

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