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Potential phytochemicals in the fight against skin cancer: Current landscape and future perspectives

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ABSTRACT

Skin cancer is a life threatening disease and their prevalence and risk has been increasing over the past three decades causing significant loss to human health worldwide. Mostly skin cancer has developed resistance against chemotherapy and radiotherapy. Therefore, development of novel, cost effective and efficient treatment methods are needed. Phytochemicals extracted from medicinal plants and dietary sources are often biologically active and has attracted the attention of researchers and pharmaceutical industries around the world. Many *in vitro* and *in vivo* studies of these bioactive compounds have shown potential antioxidant, anti-proliferative, anti-inflammatory and anti-angiogenic effects in the fight against skin cancer. These phytochemicals also regulate several other molecular processes such as angiogenesis, metastasis and cell cycle to combat skin cancer. The present review provides perspectives on the key phytochemicals, their therapeutic potentials, bioavailability and molecular mechanism of action in the cancer therapeutics. Current challenges and future directions for research are also critically discussed.

1. Cancer development: an overview

Skin is the body's largest organ, serve as a physical and chemical barrier and protect the body against harmful environmental agents such as pathogens, ultraviolet radiation (UV), chemicals and temperature fluctuations [1]. These stresses may accumulate in the body and results in skin carcinogenesis which furthermore comprises of three different stages: initiation, promotion and progression, where cancer can be interrupted using different bioactive agents (Fig. 1). The first stage, tumor initiation is a rapid process associated with exposure of carcinogens to the cells, the delivery of these carcinogens into the cells and their interaction with DNA resulting in genotoxic effect. The second stage, cancer promotion is a lengthy phase associated with proliferation of cancer cells. The third stage, tumor progression is characterized by tumor growth, metastasis and invasion into the surrounding cells [2].

Michael Sporn was the first to use the word "chemoprevention" generally referring to the use of pharmacological or natural agents (also known as chemopreventive agents (CPA) that inhibit initiation, promotion and progression of cancer. On the basis of three different stages of carcinogenesis, De Flora et al. classified CPA into three major groups [3]. Primary prevention is responsible to block tumor incidence in healthy cells by inhibiting mutagenesis, initiation and promotion. Secondary prevention is performed by inhibiting tumor progression (modulate cell signaling cascades, regulate immune system, increases

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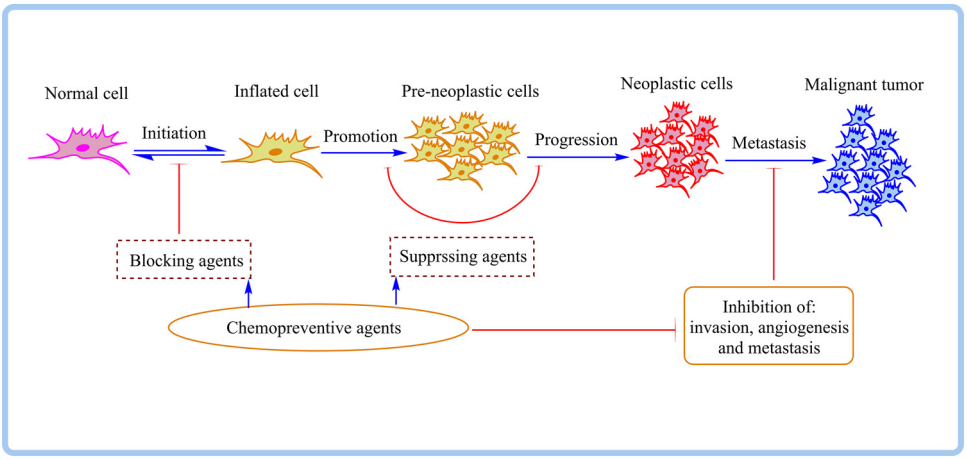

Fig. 1. Three different steps in the process of carcinogenesis: Initiation, promotion and progression. These different steps can be interfered with the help of different chemopreventive agents as for initiation (blocking agents) or for other steps of promotion and progression (suppressing agents).

antioxidant level and inhibit angiogenesis). Tertiary prevention inhibits invasion and metastasis (inhibit proteinases, activate anti-metastatic genes and modulate cell adhesion molecules) [4,5].

2. Skin cancer: a global concern

Skin cancer is a fatal disease and important public health problem throughout the world and has caused massive economic and human loss worldwide [6]. Large number of external and internal factors can stimulate the pathology of skin cancer and can worsen the situation [7]. Skin cancer is usually grouped into melanoma (MM) and non-melanoma (NMSC). NMSC is further sub-divided into basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), both develop from epidermis and contribute 70% and 25% respectively. The incidence of NMSC is higher in the Caucasians population (by as much as 18–20 times) as compare to MM [8–10]. BCC is identified by cells that are similar to epidermal basal cells and it is the least violent type [10]. BCC has shown low degree of malignancy besides local invasion, tissue damage, reappearance and low potential for metastasis [8]. The risk factors associated with BCC are age, gender, genetic diseases (Fitzpatrick skin types I and II, Gorlin-Goltz syndrome) [7]. However, UV radiations play the most significant role in stimulating BCC pathology [10]. BCC usually develops on those areas of skin which are exposed to sun, rarely on palmoplantar surfaces and never develops on the mucosal cells [10].

Moreover, SCC is known by unique proliferation of squamous cells, which can metastatize. Furthermore, SCC shows significant potential for reoccurrence, depending on tumor size, tumor lesion depth, perineural invasion, immunity system of the patient and anatomical location [2]. Some risk factors have been investigated in SCC patients such as Fitzpatrick skin type I and II, human papillomavirus type 16, 18, 31, genetic diseases such as xeroderma pigmentosum and albinism *etc* [2]. However, the most significant risk factors are UV and sunlight [11]. Generally SCC develops on those areas of skin which are exposed to sun light. It has been researched that around 55% of all the SCC arises on head and neck regions [9,10]. Additionally, SCC generally arises on the opposite sides of the hands and forearms (around 18%) [9,10]. However, around 13% of SCC cases are reported on the lags [10]. NMSC carries substantial economic burden. In Australia, it is the most expensive cancer in terms of treatment and account for AUS$ 511 million in the year 2010 [12,13]. In the USA, the total annual NMSC related costs is US$ 650 million which is 6–7 times higher than those MM treatment [14].

Another type of skin cancer is MM which is the most violent type of skin cancer develops from melanocyte located at the bottom layer of skin epidermis and mainly provide protection to skin from being exposed to external environmental factors. In addition, MM is less common among the different types of skin cancers but results in higher death rate [15,1]. Currently, each year 160,000 new cases of MM occur globally with around 48,000 deaths per year. In addition to melanocytes, malignant MM also occurs mucosal surfaces such as gastrointestinal sites, genital mucosa and oral cavity. The mortality rate associated with MM is 90% and has a survival rate of fewer than 10 years when getting into metastasis [16,17].

2.1. Skin cancer prevention

The incidence of skin cancer has been increasing worldwide [11,18,19]. This increasing incidence has been related with several factors such as such as raising awareness in the public, physicians and patients undergoing surgery with confirmed histopathology, through better registration process and long term UV exposure [20,21]. As a result of these scientists have developed different skin cancer preventive strategies and programs emphasizing the significance of skin cancer preventive measures.

Skin cancer can be prevented by adopting different measures such as primary and secondary measures. Primary prevention measures change the behavior and mindset of individuals to avoid increased sun-exposure, discourage severe sun tanning, while secondary prevention measures assist early diagnosis and detection [10,22]. Public education through awareness is one of the most important primary prevention measure. The most effective way to spread awareness among the teen boys and girls is that sun damage can results in their premature skin wrinkling [23,24]. In addition, solar radiations protection guidelines for educational institutions, media campaigns to educate public may also have profound effect on behavioral changes [25,26]. Large number of evidences suggests that several pharmacological agents may also have significant effects on preventing NMSC. There is a very strong evidence to support this notion, that vitamin D has played an important role in the progression and photocarcinogenesis of NMSC. Vitamin D 1,25(OH)2D3 and their analogs can pharmacologically modulate NMSC, is a new approach for therapeutics of NMSC [27]. Furthermore, vitamin B3 is pharmacological agent and has decreased the occurrence of NMSC by increasing DNA repair, decrease the inflammation caused by solar radiations [28,29]. The treatment of actinic keratosis with fewer negative effects and low cost may be new treatment option in immunosuppressed patients [30]. However, secondary prevention measures include, population screening for high risks, total skin self-examination and physician surveillance with aim to decrease skin cancer mortality and morbidity and diagnose cancer in their earlier stage [31].

2.2. Diagnostic and therapeutic strategies for skin cancer

Skin cancer detection and diagnosis in its early stage is highly important. High quality screening methods, earlier detection/diagnosis and novel treatment strategies has significantly dropped down the death rate [32]. Different scientists have developed different skin cancer diagnosis techniques such as, total body skin examination, optical technologies such as optical coherence tomography (OCT), high-definition (HD)-OCT, multiphoton tomography (MPT), cross polarized light and fluorescence photography, confocal laser microscope, reflectance confocal microscopy (RCM), biopsy such as, excisional, incisional, shave and punch biopsy, ultrasound (US), dermatoscopy, fluorescence, photodynamic visualization, Imaging (MRI) and computed tomography (CT) *etc* [33–37]. But still these diagnostic strategies having some limitations. There are also some novel strategies such as digitally stained multimodal confocal mosaic imaging, Raman spectroscopy, and multiphoton microscopy that are evolving state of the art techniques displaying around 99% sensitivity and 93% specificity [38,39].

Currently, many treatment strategies are available in the market for the treatment of skin cancer such as surgical excision, curettage and electrodessication (C&E), chemotherapy (includes: cisplatin, cyclophosphamide, bleomycin, doxorubicin, methotrexate and 5-FU), immunotherapy (immune modulators and monoclonal antibodies, inhibitor include, cetuximab and panitumumab), laser therapy (major laser types used are gas laser, dye laser, solid state laser and diode), radiotherapy (include, superficial radiotherapy (SRT), Electron beam radiotherapy (EBRT, Interstitial brachytherapy), cryotherapy, photodynamic therapy, treatment with topical agent (such as, piroxicam, mebutate, potassium dobesilate containing formulation, ingenol mebutate, diclofenac, imiquimod, 5-FU, betulinin acid, resiquimod, calcium dobesilate and topical retinoids *etc*), targeting skin cancer by inhibiting Hedgehog pathway with Hedgehog pathway inhibitors (such as, itraconazole, posaconazole) and ionizing radiations (IRs) *etc* [10]. However, these treatment strategies have some limitations/problems such as such as the necrosis of soft tissues or bone, pigmentary changes, atrophy, fibrosis *etc*, thus decreasing the potential of these treatment methods [40]. This situation compel researchers to develop novel and potential treatment strategies with no/less side effects. Therefore, phytochemicals have been considered as a strong chemopreventive and chemotherapeutic strategy for developing skin cancer therapeutics. Large number of medicinal plants and their potential phytochemicals have played an important role in the treatment of different types of cancers [1].

2.3. Skin cancer statistics

Skin cancer is the most common cancer worldwide. The highest rate of skin cancer incidence has been reported the individuals of New Zealand and Australia and lowest rates in parts of Africa. Worldwide, Caucasian populations have the highest risk of developing MM and Asian populations have the lowest [41,7]. In New Zealand and Australia, the annual rates of MM are 10–20 times greater than the rates in Europe for men and women respectively. The rate of incidence of NMSC is highest in Australia with more than 1000/100,000 person per year, followed by Europe 98/100,000 person-year [18,9]. BCC and SCC of the skin constitute 99% of all NMSC, with BCC more than 3–5 times higher than that of SCC [18,42]. According to 2018 statistical report by Institute of Health and Welfare Australia, it is estimated that there will be 14,320 new cases of MM (8653 males and 5667 females) in Australia and 1905 deaths (1331 males and 574 females). In 2018, the U.S alone will have 91,270 new cases of MM and 9320 deaths (5990 males and 3330 females) [6,43]. Europe alone is estimated to have 3.9 million new cases of cancer (all types, excluding non-melanoma skin cancer) and over 1.9 million deaths in 2018. According to new scientific report, New Zealand now has the highest rate of skin cancer incidence and mortality in the world overtaking Australia. The rate of incidence in New Zealand is (51/100,000) followed by Australia (49/100,000), U.S with (21.6/100,000) and then Europe with 13.2 and 13.1 per year, per 100, 000 for men and women respectively. Scandinavian countries (especially Sweden, with an estimated incidence of 23.9/100,000 in 2012), Switzerland and Great Britain report the highest rates (> 16.9/100,000 for 2012], whilst the Balkan countries, Moldova, Bosnia and Herzegovina are standing at the lower incidence levels (< 5.3/100,000 for 2012) [44].

According to Cancer Epidemiology Centre at Cancer Council Victoria the global survival rates from skin cancer is also different around the world; 99% in U.S, 92.9% in Australia, 91.8% in New Zealand, 90% in England [43]. Furthermore, this rate decreases in developing countries because of poor diagnosis and treatment facilities. In Asia, the highest rate of incidence of skin cancer cases is recorded in the Kazakhstan with 23.3/100,000 population [45].

3. Current skin cancer therapy *via* phytochemicals: a novel approach

Skin cancer is a devastating disease, therefore, novel protective and adjuvant treatment methods are needed to improve its prognosis. Medicinal plants and their bioactive compounds have been tested on many skin cancer cell lines and animal models and have shown promising anti-skin cancer results by inhibiting cancer cell development and progression [1]. The WHO has developed several dietary guidelines to decrease the risk of developing cancer. Therefore, it is highly important to educate public to consume phytochemicals as chemopreventive and chemotherapeutic agents [46]. Several epidemiological studies have shown that regular consumption of fruits and vegetables can significantly lower down the risk of developing cancer [5,47]. Several promising phytochemicals found in medicinal plants, fruits and vegetables have played significant roles in chemoprevention and chemotherapeutics of skin cancer *via* regulating different molecular processes. Detailed information about these phytochemicals, their sources and molecular processes that are regulated by these phytochemicals are given in (Figs. 2 and 3). Different phytochemicals perform different functions by inhibiting angiogenesis, metastasis, proliferation, induces apoptosis and arrest cell cycle (Fig. 4). Research and review articles for 2010–2018 were thoroughly reviewed from google scholar and ISI web of knowledge. The results are given in Fig. 5.

3.1. Ursolic acid (UA)

UA is potential phytochemical widely distributed in thyme, basil, rosemary *etc* [47]. UA has shown promising anti-proliferative, chemopreventive, antioxidant and anti-inflammatory activities. UA has induced caspase mediated cell death in MM cell lines by activating caspase-3 through mitochondria intrinsic signaling cascade, up-regulate the expression of *p53* and caspase-3 and down-regulates *Bcl-2* [48,49]. UA has also shown promising anti-proliferative mechanisms by modulating cell cycle G1 phase, modulating the expression of p21 WAF1 that regulate cell cycle [50,51]. Furthermore, in another study UA has shown to inhibit the phosphorylation of *p65* and IκBα which ultimately suppress NF-κB signaling pathway [52]. This type of UA mediated inhibition of NF-κB further decreases the expression of cyclin D1, MMP-9 and COX-2 enzymes. UA not only induce apoptosis and cell cycle arrest but has also induced UV antioxidant effect in UVB irradiated human lymphocyte as pre-treatment of UA has resulted in lower lipid hydroperoxide level and enhanced antioxidant level [53]. Scientific community is still doing huge efforts to open new avenues on their anti-skin cancer potential. But to date no clinical trials on human skin has been reported in literature. It has been demonstrated as a liposome-coating formulation, where it has been applied to three healthy subjects, which resulted in an increase in the ceramide contents of human skin [54]. However, this experimental sample size was small and was examined as

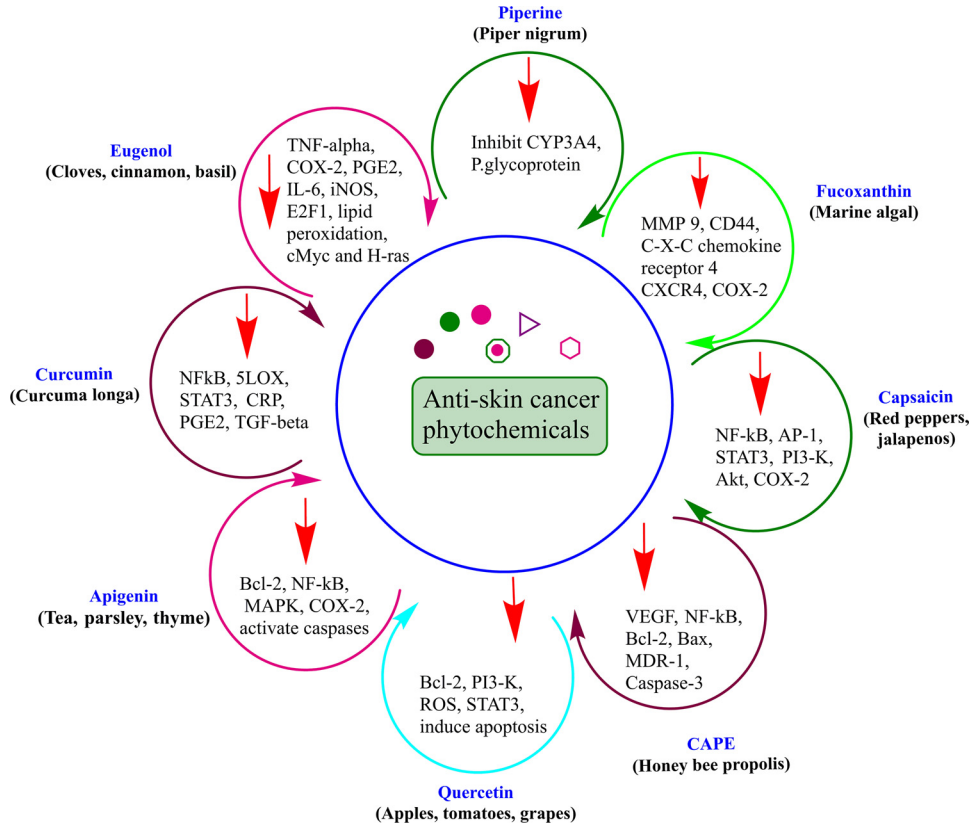

Fig. 2. Chemopreventive and chemotherapeutic of different phytochemicals against skin cancer. These phytochemicals down-regulate or inhibit the expression of different proteins, enzymes and signaling pathways to either prevent or treat skin cancer.

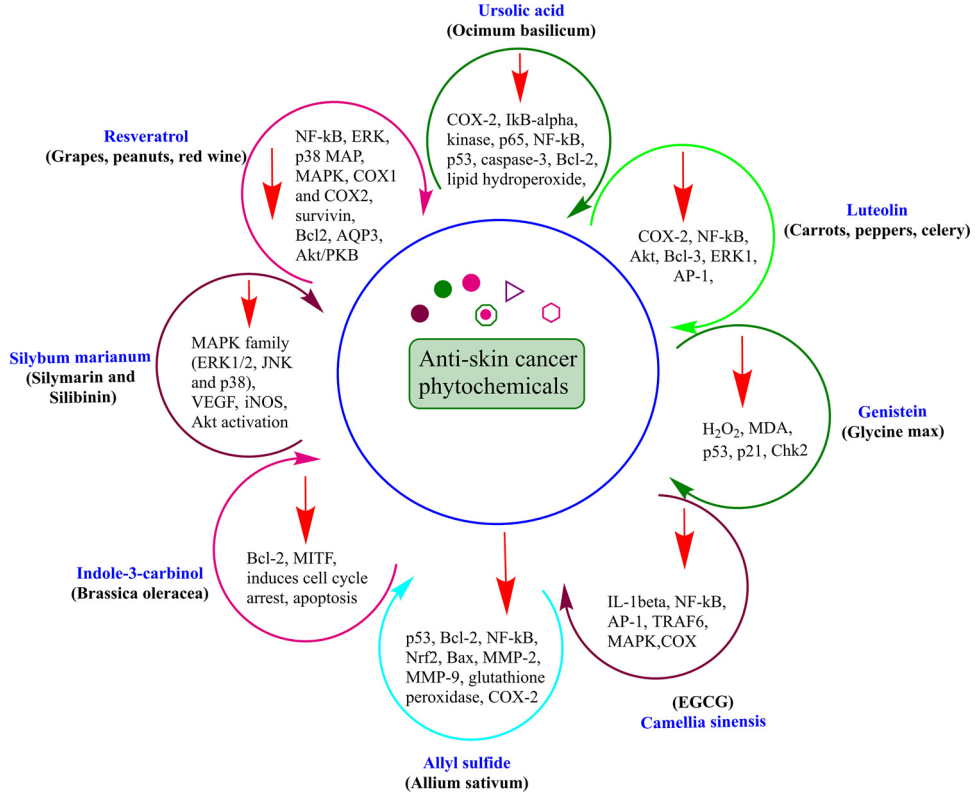

Fig. 3. Chemopreventive and chemotherapeutic of different phytochemicals against skin cancer. These phytochemicals down-regulate or inhibit the expression of different proteins, enzymes and signalling pathways to either prevent or treat skin cancer.

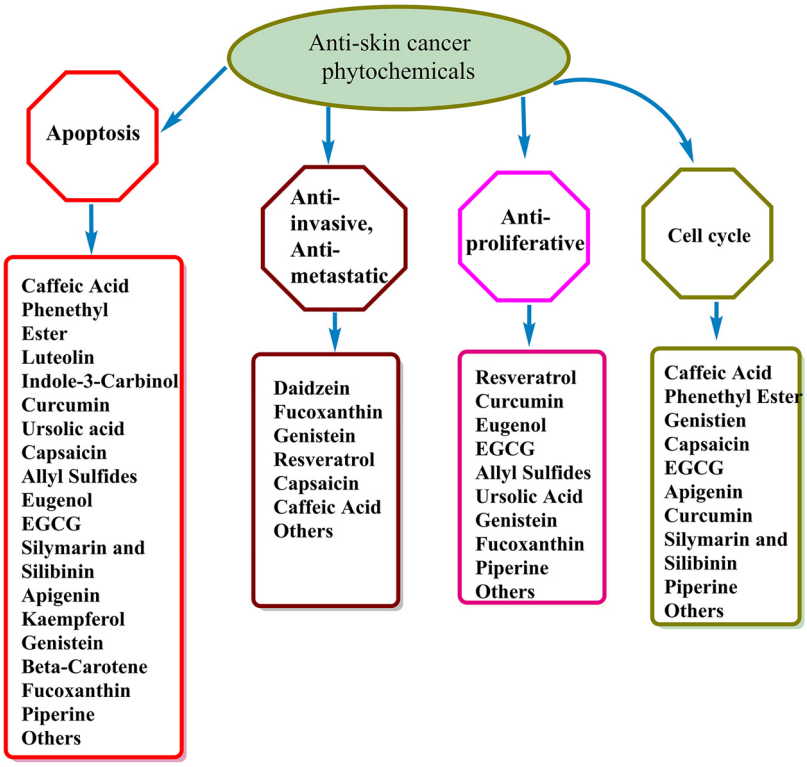

Fig. 4. Chemopreventive and chemotherapeutic effects of natural phytochemicals on different molecular processes.

a non-cancerous skin. UA still need large scale experimental human studies with skin cancer which is the need of hour.

3.2. *Caffeic acid phenethyl ester (CAPE)*

CAPE is promising active constituent isolated from honey products. CAPE has strong *in vitro* and *in vivo* inhibitory potentials in many type of cancers such as gastric, pancreatic, melanoma, lung, colon, liver and breast cancer [55–57]. CAPE has also shown strong anticarcinogenic, anti-mitogenic and anti-inflammatory properties in *in vitro* studies [58]. Additionally, CAPE has considerably inhibited the growth, invasion and migration of the skin papilloma caused by 12-*O*-tetradecanoylphorbol-13-acetate (TPA) exposure. Specifically, CAPE down-regulate vascular endothelial growth factors (VEGF) and multidrug resistance 1 (MDR-1) membrane protein. CAPE also has the potential to modulate cell cycle and has induced apoptosis *via* NF-κB [59].

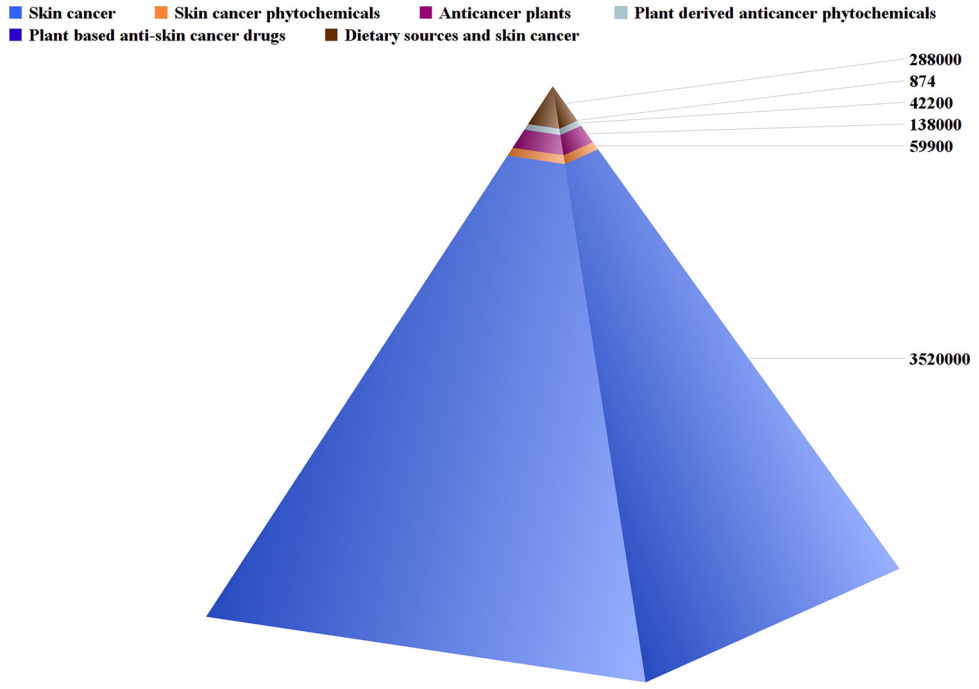

Fig. 5. Up to date Literature published on skin cancer phytochemicals. Search results of different keywords related to phytochemicals and skin cancer (2010–2018).

Furthermore, in leukemia cells, CAPE has induced apoptosis by increasing *Bax* and decreasing *Bcl-2* expression [60]. At lower concentration, CAPE has also shown antioxidant potential on mouse skin cells [61]. A very limited research work has been done on the human clinical trials of CAPE with reference to skin cancer and need further research work. However, their antioxidant, anti-inhibitory as well as inhibition of VEGF may function as a promising compound for the treatment of skin cancer.

3.3. Genistein (GEN)

GEN is a strong isoflavone isolated from soybean [62]. Soybean-rich diets been used as a dietary supplement for the treatment of cancer, heart diseases and osteoporosis [63]. GEN is widely distributed phytoestrogen in soybean having potential antioxidant, anti-inflammatory, anti-inhibitory and anti-proliferative effects [64–66]. The chemopreventive effects of GEN have been shown in a wide range of cancers such as breast, neuroblastoma and both MM and NMSC cancer [67,68]. GEN has also shown anti-angiogenic effect, reduces tumor proliferative and metastatic effect, arrest cell cycle [69] and promote caspase mediated cell death [70]. GEN has also decreased UV induced sunburn in human, protect both UV and photoaging triggered skin cancer [71]. GEN has also shown photoprotective properties in human skin by inhibiting UVB induced pyrimidine dimer formation. Furthermore, GEN also has the ability to interfere with cell cycle, by inhibiting cancer cell growth and metastasis in a xenograft models [72,73]. Pretreatment of animal exposed to UVB with GEN application suppressed UVB induced oxidative damage in the epidermis of mice through malondialdehyde (MDA) lipid peroxidation and H_2O_2 [71]. In another study GEN inhibit MM cell cycle progression by targeting *p53*, *p21*, checkpoint kinase and Chk2 [74,75]. GEN not only regulate cell cycle but also inhibit angiogenesis [76–78]. Large number of scientific evidences supporting the applications of GEN for chemoprevention and chemotherapeutic of MM and NMSC human skin cancer. GEN still need both *in vitro* and *in vivo* studies to check their route of administrations, toxicity, dosing schedule, efficacy for the management and therapeutics of cancer.

3.4. Luteolin

Luteolin is also a potential phytochemical widely distributed in carrots, celery, olives and peppers. Luteolin has shown promising anti-inflammatory, antioxidant, anti-cancer properties, inhibit angiogenesis, promote caspase mediated cell death and sensitize cells to anticancer treatments in a wide range of cancers [79]. It has been found in many research studies that luteolin induces melanogenesis and reduces aggressive effect of skin cancer cells *via* modulating β3 integrin and focal adhesion kinase (FAK) signaling cascade [80,81]. Furthermore, luteolin has shown to induce apoptosis and stop the growth of skin cancer cells by upregulating Bax, down-regulates Bcl-2 and attenuate ERK1/2 signaling [82,83]. Previous research studies of this compound has shown potential results in cancer therapeutics. However, this potential phytocompound still need further *in vitro* and *in vivo* and human clinical trials to better understand their efficacy and drug bioavailability.

3.5. Curcumin (CUR)

CUR is a strong phytocompound isolated from the rhizome of the *Curcumin longa*. CUR has shown potential anti-inflammatory and antioxidant properties in various inflammatory disorders such as psoriasis *etc* [84]. CUR also has the ability to prevent cancer by modulating 5-lipoxygenase (5-LOX), COX-2, NF-κB, STAT3, phosphorylase kinase and several apoptotic cytokines [84]. The first anticancer potential of CUR in human was demonstrated by Kuttan et al. in 1987 [85]. They found that CUR has reduced the size of cancer lesion in over 62 patients. Additionally, CUR has also shown potential role in a variety of cancer either as single agent or having strong synergistic effect with other therapeutic agents. Moreover, it has been investigated that CUR provide protection against head and neck SCC, prostate, multiple myeloma, pancreatic, lung and colorectal cancer [84]. Moreover, CUR ceases melanoma mouse model (C57BL/6 mouse) carrying melanoma while using B78H1 cells by up-regulating miRNA-2015-5p expression, which further paly very important role in modulating apoptosis and proliferation [86]. In another study, the anti-inflammatory effect of CUR has been tested against SRB12-p9 skin cancer cell line in mouse skin model. CUR administration orally to immunodeficient mice has potentially suppressed the growth of skin SCC by downregulating pS6 biomarker. CUR also has the ability to completely inhibit proliferation in RB12-p9 cell at a dose of 20 μM or above, which reflect that CUR has potential effect in skin cancer. CUR can be administered through different routes and both oral and topical administration has shown similar potential in the mouse skin model. As CUR safety and efficacy is extensively studied by different clinical trials which has made CUR a strong phytocompound for the development of different medicines/drugs against skin cancer [87].

3.6. Indole-3-carbinol (I3C)

I3C is a potential compound widely distributed in the members of family *cruciferae* which include, broccoli, Brussels sprouts and cauliflower [88]. The cancer chemoprevention properties of I3C has been shown in different cancer including breast, cervical, GIT and lung cancer [89]. It has been demonstrated that I3C enhances cell cycle arrest and apoptosis in UVB-sensitized MM cells *via* inhibiting *Bcl-2* and down-regulate microphthalmia-associated transcription factor (MITF) [90,91]. Furthermore, I3C inhibit the proliferation of human MM cells while regulating phosphatase and tensin homolog (PTEN) degradation [92]. Dietary supplementation of I3C has increased the sensitivity to chemotherapy in mouse model [93]. So far, I3C study has been confined to cellular and mouse model and these initial results need intensive scientific investigation to prove its safety and efficacy.

3.7. Resveratrol (RV)

RV is stilbene polyphenol widely distributed in mulberries, peanuts and grapes. Its topical application has strong inhibition potential on all three different stages of carcinogenesis in murine model [94,95]. It has shown strong anti-cancer effect by possessing anti-proliferative, anti-inflammatory and antioxidant potentials [96], and act as strong scavenger for ROS [97] and has potentially reduced ROS level in human skin fibroblast cell *in vivo* [98]. Despite, to its antioxidant property RV also antagonize anti-inflammatory action by hindering the effect of *COX-1 in vivo* [94] and *COX-2* in mouse skin [99] mainly by inhibiting the expression of NF-κB and suppress both *p38* MAPK and ERK [96,100,101].

RV may also have shown strong potential with other phytocompounds by suppressing tumorigenesis and reducing murine epidermal hyperplasia while decreasing the expression of proteins such as p21 COX-2, Bcl-2 and enzymes [102]. RV may also function as an adjuvant with other chemotherapeutic agents in the treatment of MM with distant metastatic disease where RV has potentially decreased skin cancer cells viability and increased the cytotoxic effects of temozolomide on cancer cells [103]. Additionally, RV has the ability to suppress the activity of redox factor-1 (Ref-1), rendering skin cancer cells more sensitive to the alkylating drug dacarbazine [104]. Furthermore, the expression of Akt/PKB proteins in MM cells is another phenomena by which RV show chemotherapeutic effects on MM skin cancer [105].

Furthermore, RV orally has shown poor bioavailability *in vivo* because of its fast clearance by liver and intestine causing reduced concentration in the human body [96]. This may limit RV contact to the skin cells and tumor showing its inability to stop cancer proliferation when administered orally to mice incorporated with skin cancer [101]. Therefore, topical administration of RV may be highly promising for

chemoprevention and chemotherapeutics. Presently, topical applications of cream having RV has shown potential improvement in elasticity, hydration and luminosity of skin without any negative effects in normal people [106]. In addition, in one more study performed on 55 patients, combination of RV with baicalin and vitamin E enhanced the photodamaged skin in around 12 weeks [107]. These clinical trials are performed on small sample size and have investigated non-cancerous skin. While their potential efficacy and safety in both MM and NMSC prevention and treatment need huge clinical trials and initial results have shown potential effects. Scientific community is still engaged in investigating their further pharmacological potential and is expecting to open new avenues.

3.8. [6]-Gingerol

[6]-Gingerol is pungent phenol phytocompound extracted from the root of *Zing*iber *officinale*. The first study on [6]-gingerol was perform in by Park et al. 1998 where the topical administration has potentially inhibited skin papilloma formation [108]. Moreover, [6]-gingerol has also induced anti-inflammatory activity by decreasing the activity of epidermal ornithine decarboxylase, inhibit *COX-2* and suppress NF-κB *via* modulating p38 mitogen-activated protein kinase (MAPK) activity [108,109]. Furthermore, [6]-gingerol has also inhibited antioxidant activity by decreasing UV radiation induced intracellular ROS level, activate caspases-3, 8, 9 [110].

Many other strategies include the activation of AP-1 DNA binding activity [111], modulate proteins such as p53, Bax, Bcl-2 and survivin [112]. Up to date no research work has been published on human trials and investigation is going on to incorporate [6]-gingerol into solid nanoparticles for topical administration to enhance their safety, efficacy and stability [113]. This type of delivery system for [6]-gingerol may be helpful to provide more easy and stable option for additional human clinical studies.

3.9. Capsaicin

Capsaicin is a promising bioactive compound extracted from red pepper and red chili pepper. There are controversial scientific evidences whether capsaicin function as a carcinogenic agent or for the chemoprevention and chemotherapeutic purposes [114]. Hwang et al. demonstrate that the topical use of capsaicin stimulated skin cancer in mouse model treated with TPA, indicating that capsaicin is pro-carcinogen by activating tyrosine kinase EGFR and COX-2 [115]. However, other researchers had come up with opposite results and found that topical use of capsaicin has caused no substantial increase in the growth of mice skin cancer compared to controls and even significantly inhibited papilloma formation in mice thus inhibiting skin cancer [116]. The capsaicin has shown strong chemopreventive and chemotherapeutic properties by arresting cell cycle, induces apoptosis and inhibit cancer cells proliferation by antagonizing NF-κB, AP-1, STAT3 and COX-2 expression [117]. Furthermore, capsaicin has also shown its therapeutic potential by inducing caspase mediated cell death in human cutaneous SCC cell line *via* inhibiting mitochondrial activity [118]. While other research studies indicate that capsaicin has the anti-mitogenic activity on metastatic MM cells by down-regulating the expression of phosphatidylinositol 3-kinase (PI3-K) [119]. Capsaicin also possess synergistic effects by inducing caspase mediated cell death in MM cell lines when applied in combination with HA14-1 [120]. Scientists are also doing further research work and epidemiological studies to better confirm the role of capsaicin for the therapeutics of cancer.

Although no previous studies have better explained the topical application of capsaicin in the treatment of skin cancer, we can conclude from the experience of topical use of capsaicin in other areas. According to one comprehensive review which had found that one out of three patients administered with capsaicin had a higher rate of side effects as for examples stinging, erythema, burning compared to placebo [121]. These negative side effects are potential drawbacks for the topical use of capsaicin in the chemoprevention and chemotherapeutics of skin cancer. Therefore, novel drug delivery system, designing and formulations of capsaicin with other agents having no/less side effects will be a new modality for treatment of skin cancer.

3.10. Caffeic acid (CA)

CA is also a promising polyphenolic compound widely distributed in coffee, fruits and vegetables. CA is a bioactive phytocompound with potential antioxidant, anti-inflammatory and anti-cancer potential [122–124]. Furthermore, Yang et al. found in his study that CA can potentially inhibit colony formations and EGF-induced tumor in keratinocyte cell [125]. Additionally, CA attenuate the migration ability of cancer stem cells by increasing p38 phosphorylation and deactivate NF-κB/snail signaling cascade. Actually, p38 reduces the DNA-binding activity of NF-κB to promoter of snail gene which ultimately result in the deactivation of transcription of snail. Moreover, impaired epithelial mesenchymal transition (EMT) has been noticed in CA treated human keratinocyte tumor. EMT is a mechanism through which epithelial cells lose their polarity and gain migration and invasion properties. The E-cadherin level increases while N-cadherin and vimentin level decrease in CA treated malignant human keratinocyte cells. These results show that CA provide protection to cancer cells against invasion and migration [126,125]. Scientific community is still optimistic to develop new formulation from these compounds to provide skin cancer patient with the best treatment option.

The topical use of CA on dorsal surface of UV induced skin cancer mice model inhibited the incidence of cancer [126]. The MAPK signaling pathway involves several other molecular pathways of which Ras-Raf-MEK-extracellular signal regulated kinase (ERK) 1/2 cascade is most frequently regulated in human cancers. This molecular process regulate many other functions of the cell such as cell growth, cell proliferation [127]. CA also suppress ERK1/2 functions in *in vitro* and caused chemotherapeutic functions against UV induced skin cancer [126]. In addition to MAPK, they also found to increase the expression of *COX-2* and Fyn kinase in UV induced skin carcinogenesis. CA can also potentially suppress UVB induced *COX-2* expression by interfering with the activity of NF-kB and AP-1 which consequently inhibit prostaglandin E2 and block Fyn kinase activity in a mouse model of skin cancer [128].

Furthermore, Chao et al. found that CA can possess anti-inflammatory property by down-regulating the expression of IL-1β mRNA and TNF-α, IL-6 and protein in heart tissue of diabetic mice [129]. Moreover, in another study Song et al. observed that CA has anti-inflammatory potential by decreasing the activities of phospholipase A2 and myeloperoxidase (MPO) in skin-induced mouse [130].

CA could also potentially decreased the expression of mRNA and proteins of IL-1β, TNF-α, and IL-6 at the targeted site and also in *in vitro* human keratinocytes [131]. These findings indicate that CA has strong anti-inflammatory role while blocking the synthesis of cytokines and MPO activity. Overall, these findings can be used as a guide for the development and testing of CA for their strong therapeutic potential in clinics for skin cancer.

3.11. Eugenol

Eugenol is a phytochemical (phenol) mainly distributed in cloves, mutmeg, bay leaves, basil and cinnamon. It can be administered into the body through different routes. Topical use of eugenol and oral delivery of an aqueous infusions of cloves into mice having skin cancer reduced the incidence of papilloma development [132]. Furthermore, eugenol also possess anti-proliferative and antioxidant activities through different mechanisms. Eugenol perform its antioxidant activity by rapid scavenging, inhibit ROS formation and lipid peroxidation [132]. Additionally, topical use of eugenol may reduce inflammation by

inhibiting COX-2 enzyme, induce nitric oxide synthase (iNOS) expression, decreases the level of TNF-α, IL-6, PGE2 and modulate the expression of NK-κB [133]. Furthermore, eugenol decreases the expression of oncogenes, H-ras and *c-Myc*, modulate p53 expression and induces apoptosis by lowering the synthesis of E2F1 transcriptional factor [134,135].

Recently, eugenol was formulated as a nanoemulsion for topical anti-inflammatory use in murine skin, with 2% eugenol formulations showing better anti-inflammatory activity compared to topical piroxicam after 1.5 h [126]. Additional *in vitro* and *in vivo* skin permeation trials are needed to better explain the anti-inflammatory, antioxidant and anti-cancer effect of eugenol and then to develop new formulations.

3.12. Epigallocatechin-3-Gallate (EGCG)

EGCG is potential phytocompound isolated from *Camellia sinensis* and is the widely studied chemopreventive and chemotherapeutic constituent of green tea phenols (GTP) with anti-inflammatory, anti-proliferative and antioxidant potentials [136]. One of the eminent scientist Katiyar et al. have performed great research work on GTP and investigated that GTP perform its anti-inflammatory activity by inhibiting COX and lipoxygenase activity, lower skin cancer load by decreasing epidermis hyperplasia and edema [137]. They later on work on antioxidant potential of EGCG on human skin cancer by topical use and has significantly reduced UV radiations induced ROS products [138]. These radiations are also associated with the inhibition of MAPK signaling cascades [139]. Other anti-proliferative functions performed include the modulation of NF-κB signaling cascades [140,141], inhibit tumor induced activator protein (AP-1) [142], inhibit angiogenesis and recruit T cells [143].

Furthermore, Nihal et al. have demonstrated that EGCG sensitizes MM cells to interferon induced growth inhibition, reduces cancer cell proliferation and induces caspase mediated cell death [144]. They came up with unique results that the synergistic effect of EGCG along with interferon was highly effective than that of their application alone. EGCG also downregulates inflammation, which leads to decrease in interleukin (IL)-1β secretion and down-regulate NF-κB activity resulted in reduced cancer cells growth [145]. In recent studies scientist have also demonstrated, that EGCG also inhibit MM cell invasion by decreasing the function of tumor necrosis factor (TNF) receptor associated factor 6 (TRAF6) [146].

EGCG has shown strong therapeutic potential for the chemoprevention and chemotherapeutics of skin cancer in different human trials. The topical verses oral application remains a key issue. Scientists have observed that mice orally administered with GTP or *via* injection either inhibit or reverse UV-induced skin papillomas [147]. However, according to another research which demonstrate that tumor inhibition in mice was only noticed by applying topical administration of EGCG but not through oral [148]. A study of humans administered with topical GTP confirmed that it provide protection against UV radiation induced erythema [149]. However, according to another single-blind randomized clinical trial on 50 individuals confirmed that healthy individuals who had taken GTP orally with vitamin C did not considerably reduced skin leukocyte infiltration and erythema as compared to placebo group [150]. The scientific community assumed that their topical administration may not be active in the skin cancer formulations due to their poor bioavailability. These research studies conclude that the topical use of EGCG is highly potential than that of oral application for skin cancer chemoprevention and chemotherapeutics and need further research work.

3.13. Silymarin and silibinin

Silibinin is also a promising phytochemical isolated from the seeds of Milk thistle. Silibinin is the main bioactive part of silymarin complex. The applications of silibinin has been restricted because of poor bioavailability. However, scientists are trying to develop new formulations for their better absorption in the form of nanosuspensions [151]. Silymarin has performed several biological functions for the therapeutics of liver diseases, act as scavenger for ROS, phenylglyoxylic ketyl radicals [152]. Different other clinical trials have been investigated for the chemotherapeutic effects of silymarin on a wide range of cancers including skin cancer [153]. One study confirmed that silymarin perform cancer chemotherapeutic activity by inhibiting TPA induced tumor promotion in mouse skin. Another research study reported that silibinin target the CDKs pathway performing strong anticancer activity by arresting cell cycle [154]. Additionally, silibinin antagonizes angiogenesis by targeting VEGF receptors and iNOS [155,156]. Moreover, silibinin also induce caspase mediated cell death through extrinsic and intrinsic signaling pathways [157,158].

Furthermore, Katiyar et al. reported that silymarin provide protection against UV radiations induced skin cancer in a mouse model of photocarcinogenesis [159,160]. In addition, silymarin administration inhibit UVB-induced sunburn, skin edema, induce apoptotic cell formation, decreases catalase activity, and induce COX and ornithin decarboxylase expression. The same protective effects were also reported in application of silibinin on UVB-damaged skin such as proliferating cell nuclear antigen, thymidine dimer-positive cells, and apoptotic sunburn cells were decreased after silibinin treatment [161]. The silibinin has also shown potential role in targeting MAPK-mediated signaling cascade cancer therapeutics [162,163]. Both dietary intake and topical application of silibinin inhibited MAPK, *p38*, JNK and Akt activation induced by UV exposure in SKH-1 mouse skin [164]. Further, study reported that silymarin has significantly decreased the accumulation of β-catenin in human MM cells, thus inhibiting MM cell migration [165,166]. Collectively, these findings suggest that silymarin/silibinin has proven as strong chemopreventive and chemotherapeutic agents against skin cancer. Future human cancer clinical trials of silymarin can also be focused on their toxicity and bioavailability which need deep scientific investigation.

3.14. Allyl sulfides (AS)

Allyl sulfides comprised of diallyl sulfide (DAD), diallyl disulfide (DADS) and diallyl trisulfide (DATS) are potential phytocompounds mainly distributed in garlic. Research studies have demonstrated that they have potential anti-inflammatory, antioxidant and anti-cancer activities against skin cancer. Previous study conducted on the potential of garlic derivatives have shown, that the topical use of garlic has significantly reduced the incidence and growth in mouse skin [167]. Later on different other studies confirmed the chemopreventive and chemotherapeutic potential of topical AS in inhibiting skin cancer in murine model [168–170]. Different strategies have been proposed for the chemoprevention effects of AS. Topical use of DAS have shown potential role to regulate the expression of *p53* in mice with skin cancer [171,172]. DAS has the ability to significantly reduce the tumor *via* inducing caspase mediated cell death in mice skin [173].

Furthermore, DAS may also possess chemopreventive and chemotherapeutic effects by regulating multiple signaling pathways, as for example, down-regulate H-ras mRNA *via* inhibiting oncogenic *p21* expression [174], up-regulate p53 and Bax proteins, down-regulate PI3K/Akt and MAPKs [175]. Recent studies have confirmed that DAS is greatly helpful against UV radiation induced skin cancer development in mice by regulating several molecular targets such as NF-κB, PEG2, *COX-2* and *p53* [176].

Similar results have been shown by DADS where its topical application have reduced the incidence of skin cancer and multiplication in mouse model of skin cancer [177]. Shan et al. in his research study confirmed that DADS has up-regulated several antioxidant enzyme such as glutathione peroxidase, catalase and superoxide dismutase. The study also revealed the potential of DADS in epidermis by up-regulating the expression of p21 protein, allow Nrf2 to play significant role to

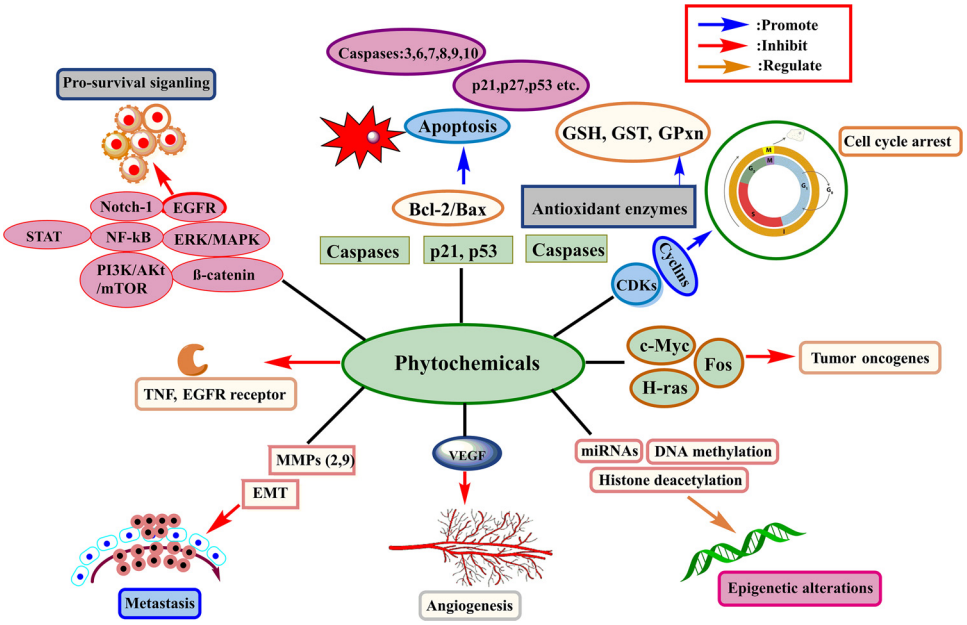

Fig. 6. Different phytochemicals involved in regulating a wide range of molecular processes in order to modulate skin cancer. Detailed information are given in the main text.

maintain cellular redox homeostasis. DATS are also potential compounds and have shown potential effects by reducing the occurrence and multiplication of skin papilloma by suppressing the expression of COX2 *via* regulating JNK or Akt signaling cascade [178]. DATS also induced apoptosis in MM cells by decreasing Bcl-2 and Bcl-xl expression [179]. The same results were also revealed in human BCC cells, where DATS triggered caspase mediated cell death by up-regulating p53 and Bax expression level and lower down Bcl-2 and Bcl-xl expression. These results show that DATS induces endoplasmic reticulum stress in cancerous cells which leads towards cell death [180]. Currently, DATS has also shown potential role in inhibiting human MM cell invasion and migration by down-regulating MMP-2 and MMP-9 expression, inhibit adhesion by disrupting the integrin signaling pathway [181].

While comparing the potential of different AS, one research study demonstrated that DATS have shown higher potential in inhibiting COX-2 expression that of DADS and DAS in human embryonic cell kidney cells [182]. Furthermore, DATS have shown strong inhibition results in human MM cells and BCC cell line that of DADS and DAS [183]. The study also investigated that AS can inhibit cancer cell growth while arresting G2/M phase, induces caspase mediated cell death, activate *p53* pathway in response to oxidative stress [183]. In nutshell, DATS is highly potential chemopreventive and chemotherapeutic phytocompound than that of DATS and DAS. Up to date no human clinical trials have been reported and need further pharmacological and bioavailability studies.

4. Challenges for phytochemicals and future directions

There are many challenges that phytochemicals are facing. The primary challenge is the bioavailability of these phytochemicals. As large number of these phytochemicals are consumed in our daily diet, they are easily digested and removed by our body, thus having short lived therapeutic efficacy [184]. Scientists are trying to develop new strategies that will be helpful in increasing their stability. These strategies include development of stabilizers, coating/capping of phytochemical into a specific type of system, such as microparticle or nanoparticle that can potentially enhance their stability and antioxidant properties [185]. Scientists have investigated that coating of green tea extract with chitosan nanoparticle is very helpful in stabilizing phytochemical EGCG and has resulted in significant absorption in the intestine [186]. Another example is coating of catechins and epicatechins with bovine serum albumin nanoparticle (BSA-NPs), has also potentially enhanced their antioxidant potentials and stability [187].

Another challenge of phytochemical in cancer therapeutic is the absence of target specificity. Different research studies have revealed that these phytochemicals are having pleiotropic effect as a result cancer cell often activate different other molecular pathways resulting in the failure of targeted therapeutics [188]. There are several alternative strategies to deal with these problems, including formulations of semi synthetic derivatives and analogs for improving phytochemicals safety, efficacy and bioavailability, novel formulations for targeted delivery of phytochemicals, development of new delivery systems that can assess the protective properties, pharmacokinetics and bioavailability of these phytochemicals in human body. For topical skin cancer formulations, challenges such as potential skin penetration, drug concentration, stability and length of treatment method, sustained drug release through topical application system need further scientific investigations.

5. Conclusion and future outlook

The phytochemicals isolated from medicinal plants and dietary sources have shown great potential on different *in vitro* cell lines and *in vivo* experimental animal models. Many epidemiological studies have also reported inverse relationship between dietary phytochemicals (fruits, vegetables) and skin cancer. Phytochemicals are natural antioxidants, increases the expression of antioxidant enzymes, cyclins, CDKs, p21, p53 and Bax proteins, scavenge ROS, modulate various signaling pathways such as, NF-kB, Notch-1, EGFR, ERK/MAPK, STAT, ß-catenin, PI3K/AKt/mTOR, inhibit the expression of oncogenes such as c-Myc, H-ras, Fos genes, down-regulate Bcl-2 and Bcl-xl.

Phytochemicals can prevent skin cancer proliferation by inducing apoptosis, down-regulate the expression of anti-apoptotic factors (Bcl-X_L, X-IAP), regulate iNOS and COX-2. Phytochemicals can also inhibit skin cancer cells by inhibiting angiogenesis and metastasis, arrest cell cycle, suppress EMT, regulate epigenetic alteration, down-regulate MMPs and COX-2 enzymes (Fig. 6). Overall, these phytochemicals may potentially protect or reverse the damaging effects caused by UV radiations and other noxious environmental carcinogens.

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