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Review

Plant derived anticancer agents: A green approach towards skin cancers

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ABSTRACT

Plants have been used as medicinal agents since the origin of mankind. High cost and severe side effects associated with conventional chemotherapy has limited their general acceptability and fuel up the search for alternate options. The alternative treatment options like phytochemicals have come up with ease of availability and cost effectiveness. Owing to their general acceptance, safety, low side effects and multistep targeting in signal transduction pathways, plant derived phyto-constituents have promising anti-carcinogenic potential for skin related cancers. This leads to the surge in research of new phytochemicals for the prevention and cure of a variety of skin cancers which are major cause of morbidity and mortality in present world. Although very limited clinical data involving humans is available in literature to demonstrate favorable eff ;ects of phyto-constituents on various types of skin carcinomas yet the topical treatment with these plant derived anticancer phytochemicals is very promising. There are various mechanisms and pathways responsible for antitumor activity of plant derived medicinal compounds such as loss of mitochondrial membrane potential, release of cytochrome-c, Down regulation of Anti-apoptotic proteins and Up regulation of pro-apoptotic proteins, Activation of Caspase, Fas, FADD, p53 and c-Jun signaling pathway, Inhibition of Akt signaling pathway, phosphorylation of ERK, P13K, Raf, survivin gene, STAT 3 and NF-kB. *In-vitro* testing of skin cancer cell lines models offers the opportunity for identifying mechanisms of action of compounds from plant origin against variety of skin related cancers. This review thus aims at providing an overview of plant derived anti-cancer compounds which have been reported to show promising anti-carcinogenic effects against various skin cancer cell lines and on animal models. Phytochemicals that are discussed in this review include steroids, coumarines, trepenes, essential oils, alkaloids, esters, ethers, resins, phenols and flavonoids. This review also provides information about marketed formulations developed so far from plant derived compounds for skin cancer prevention and treatment.

1. Introduction

Cancer is a molecular alteration in the human DNA that leads to the altered biochemical and physiological functions of the body [1]. It is the second leading cause of mortality and is responsible for 1 out of 6 deaths globally. (http://www.who.int/mediacentre/factsheets/fs297/en/) Skin cancer has evolved as the most common malignant disease accounting 4.5% of all new cancer cases [2] with an average increment of about a million new cases annually [3]. This prevalence is more than any other cancer type [4]. This alarming and frightful rise in mortality rate due to various types of skin cancer has provoked the pursuit for efficacious anticancer agents with lesser side effects to combat this disease. Because the eventual goal of anticancer therapy is the hunt of selective chemotherapeutic agents that only kill or render the malignant tumor cells to benign without any effect on normal cells [5]. But current chemotherapeutic agents being used in oncology are, unfortunately, toxic to normal cells. So the newer, effective and nontoxic compounds isolated from natural sources like phytochemicals with anticancer activities are need of the hour [6]. Plants have been used as medicinal agents since the origin of mankind. Plant derived medicinal agents have several advantages as for as the availability is concerned. They are being used as cure as well as preventive agents for a number of deadliest diseases like AIDS, hepatitis and cancers [7]. This leads to the surge in research of new phytochemicals for the prevention and cure of a variety of cancers. The alternative treatment options like phytochemicals have come up with ease of availability, less toxicity and cost effectiveness [1]. The hunt for plant derived anticancer agents was initiated in the 1950's when the anticancer properties of Vinca alkaloids

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Table 1
Phytochemical against various skin cancer cell lines.

S/No	Phytochemical	Plant Name	Part use	Skin cancer cell line	Mechanism	References
1	4-nerolidylcatechol	*Pothomorphe umbellate* (Piperaceae)	Whole	SK-MEL2, SK-MEL103, SK-MEL147	G-1 phase arrest, inhibit the effect of matrix metalloproteinase MMP-2 and MMP-9 activity, loss membrane integrity	[54]
2	[6]-Gingerol (phenolic ketone)	*Zingiber officinale*	Rhizome	Human epidermoid carcinoma cells A431	Mitochondrial membrane depolarization i.e. loss in membrane potential, increase Bax/Bcl-2 ratio, release of cytochrome c into cytosol, activation of caspase-3, -9 and Apaf-1	[55]
3	Acacetin (flavonoid)	*Robinia pseudoacacia* (Fabaceae)	Whole	SK-MEL5, SK-MEL28 in mice	Suppress Akt/p70S6K signaling pathway, inhibit P13K activity	[56]
4	Apigenin (flavonoid)	*Lycopodium clavatum*		Human keratinocyte cell line HaCaT	Inhibit the formation of ROS, interfere with NF-kB and p38MAPK signaling pathways	[57]
5	Arnidiol	*Barleria longiflora* (Acanthaceae)	Stem	Melanoma (LOX IMVI, MALME-3M, M14, SK-MEL-2, SK-MEL-28, SK-MEL-7, UACC-257, UACC-62)	–	[58,59]
6	Betulin and acetylenic derivative 28-*O*-propynoylbetulin	*Betula alba* (Betulaceae) *Betula pendula* (Betulaceae) *Betula pubescent* (Betulaceae) *Betula platyphylla* (Betulaceae)	Bark	Melanoma SK-MEL 28, SK-MEL2, G361	Effect on human melanocortin (MC) receptor signelling pathway, inhibit melanocyte stimulating hormone and downregulate MC1 receptor responsible for differentian and proliferation of epidermal melanocytes, Loss mitochondrial membrane integrity, activation of Caspase-3	[60,61]
7	Buchariol and naringenin	*Salvia Leriifolia* (Lamiaceae)	Aerial parts	Melanoma A375	–	[62]
8	Cucurbitacins (cucs) and derivatives (cucurbitacin D and J)	*Cucumis sativus* (Cucurbitaceae)	Fruit	Melanoma SK MEL28, A-375	Inhibit phosphrylation of ERK and also effect the total level of ERK, downregulate the MAPK signaling pathway	[63]
		Helicteres angustifolia (Sterculiaceae)	Roots and stem	Melanoma SK-MEL28	–	[64]
9	Cyclodione (Menadione, stigmasterol)	*Mesua beccariana* (Clusiaceae)	Stem bark	SK-MEL28	–	[65]
10	Elenoside (Arylnaphthalene Lignan)	*Justicia hyssopifolia* L (Acanthaceae)	Leaves	LOX IMVI; MALME-3M; M14; M19- MEL; SK-MEL-2; SK-MEL-28; SK-MEL-5; UACC-257	–	[66]
11	Epigallocatechin-3-gallate	*Camellia sinensis*	Leaves	A-375 and Hs-294T melanoma cells	Cell cycle G-phase and S-phase arrest in A-375 and Hs-294T melanoma cells respectively, inhibit the protein expression of cyclin-D1 and cdk-2, downregulate the expression of anti-apoptotic protein and increase the expression of Bax, activate the caspase -3,-7 and -9	[67]
12	Essential oils (linalool, β-caryophyllene and α-cedrol)	*Cupressus sempervirens* L. (Cupressaceae)	Leaves	Amelanotic melanoma cell line C32	Not clearly understood	[68]
13	Extract (silver nanoparticle)	*Moringa oleifera* (Moringaceae) *Acorus calamus* (Acoraceae) *Cucurbita maxima* (Cucurbitaceae)	Leaves Rhizome Petals	A-431 epedermoid carcinoma cell lines	–	[69]
14	Fisetin (flavonol)	*Malus domestica* (Rosaceae), kiwi, strawberry	Fruit	Mel 928 and 451Lu human melanoma cells	Downregulate frizzled, LRP6 and upregulate Axin tranmembrane receptors, dephosphorylation of GSK3β, inhibit the expression of Akt by inhibiting the phosphorylation of Ser^{473} and Thr^{308}, upregulate the expression of b-TrCP expression. Inhibit the proliferation of melanoma cells by Wnt/ β-catenin pathway, reduce the level of β-catenin and Mitf	[70]
				Human melanoma cells A375, RPMI-7951 and Hs294T	Inhibit the migration of NF-kB P65 and P50 to nucleus and phosphorylation of MEK ½ and in turn phosphorylation of ERK ½, downregulate the expression of IKKα and inhibit the phosphorylation of IkBα, upregulate the expression of E-cadherin and decrease the expression of desmoglein (involved in the formation of desmosomes), vimentin (an intermediate filament), snail (transcriptional repressor of E-cadherin expression) and fibronectin (extracellular matrix protein).	[71]
				Human epidermoid carcinoma A431 cells and human squamous carcinoma SCC-13 cells	Cell cycle arrest at G_2/M phase, downregulate the expression of anti-apoptotic protein and upregulate the expression of pro-apoptotic proteins, loss mitochondrial membrane integrity and turn decrease the level of mitochondrial cytochrome c and Smac/DIABLO, increase the expression of caspase-9, 7 and 3.	[72]

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