Curcumin: A new candidate for melanoma therapy?

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Abstract

Melanoma remains among the most lethal cancers and, in spite of great attempts that have been made to increase the life span of patients with metastatic disease, durable and complete remissions are rare. Plants and plant extracts have long been used to treat a variety of human conditions; however, in many cases, effective doses of herbal remedies are associated with serious adverse effects. Curcumin is a natural polyphenol that shows a variety of pharmacological activities including anti-cancer effects, and only minimal adverse effects have been reported for this phytochemical. The anti-cancer effects of curcumin are the result of its anti-angiogenic, pro-apoptotic, and immunomodulatory properties. At the molecular and cellular level, curcumin can blunt epithelial-to-mesenchymal transition and affect many targets that are involved in melanoma initiation and progression (e.g. BCl2, MAPKS, p21 and some microRNAs). However, curcumin has a low oral bioavailability that may limit its maximal benefits. The emergence of tailored formulations of curcumin and new delivery systems such as nanoparticles, liposomes, micelles and phospholipid complexes has led to the enhancement of curcumin bioavailability. Although *in vitro* and *in vivo* studies have demonstrated that curcumin and its analogues can be used as novel therapeutic agents in melanoma, curcumin has not yet been tested against melanoma in clinical practice. In this review, we summarized reported anti-melanoma effects of curcumin as well as studies on new curcumin formulations and delivery systems that show increased bioavailability. Such tailored delivery systems could pave the way for enhancement of the anti-melanoma effects of curcumin.

Key words: Curcumin, Melanoma, Therapy, Cancer

Introduction

Plant extracts and their active compounds have long been regarded as promising candidates to treat a variety of human diseases; however, natural products or their synthetic analogues may cause serious side-effects, (1, 2). Since natural products generally show less toxicity than synthetic compounds, they have been the subject of increasing research interest particularly for the treatment of cancer and its complications (3, 4). Curcumin is a natural polyphenol extracted from the rhizomes of the plant *Curcuma longa* L. (turmeric) (5, 6). Mounting evidence indicates that curcumin plays significant roles in several biological processes and possesses several pharmacological properties which are beneficial to the treatment of human diseases. These pharmacological effects include antioxidant (7-10), anti-inflammatory (3, 11-13), lipid-modifying (14-17), anti-arthritic (10, 18), cardio-protective (19, 20), anti-ischemic (21), anti-depressant (6, 22), anti-diabetic (23), neuro-protective (24), cognition-enhancing (25-28), and anti-atherosclerotic (5, 29) properties. These studies confirmed that curcumin can affect various targets such as cytokines, protein kinases, multiple transcription factors, adhesion molecules, inflammatory mediators and redox state enzymes (5, 30).

Melanoma arises from malfunctioning of normal melanocytes in the epidermis. In recent decades, the incidence of melanomas has increased at an alarming rate, particularly in Western populations where individuals tend to have lighter skin color and thus less sun protection (31-33). Patients with advanced malignancies have poor prognoses with average survival times of 3-11 months (31). Many melanomas with early diagnoses can be removed by surgical resection with no further problems to the patient. However, melanomas notoriously have high metastatic potential, and once metastasis occurs, they are very difficult to treat (31, 34). Therefore, the search for novel therapies against melanoma is warranted. Many studies introduced curcumin as

a novel molecule that can be used for the treatment of melanoma (35, 36). These reports have employed curcumin and its analogues using various delivery systems in melanoma therapy (36, 37).

With respect to the pharmacokinetic profile of curcumin, it has been observed that utilization of novel delivery systems such as micelles and nano-particles could increase curcumin bioavailability, thereby potentiating its anti-tumor effects in melanoma. In addition, the expression of certain microRNAs, known to influence many molecular and cellular processes, can be altered by curcumin (38, 39). This review summarizes the findings of various studies on the utilization of curcumin in melanoma therapy. Research on the tailored formulations with novel drug delivery systems, and synthetic analogues of curcumin are also discussed.

Curcumin as a therapeutic agent in melanoma

For hundreds of years, turmeric has been utilized as a treatment for conditions like inflammation, neoplasm, etc (3, 5). In recent years, molecular targets and various cellular and molecular pathways that are affected by curcumin have been evaluated and identified (5, 40).

Several studies on animals and humans have indicated that curcumin can be safe at various doses (41, 42). These reports showed that curcumin could be tolerated even at very high doses. Although obtaining high doses of curcumin in humans is a problem, with the help of novel drug delivery systems, the problem of using bulky doses could be resolved (43). In addition, various studies have indicated that even low doses of curcumin have therapeutic effects against various diseases (44).

Low solubility and lack of a high systemic bioavailability is regarded as a major problem in utilization of curcumin as a therapeutic agent (45). Several studies have reported low or

undetectable plasma/tissue levels of free curcumin (46, 47). However, it must be taken into account the metabolites and degradation products of curcumin, like curcumin sulfate, curcumin glucuronide and tetrahydrocurcumin possess significant and, in some cases, similar or stronger biological and pharmacological activities compared with curcumin (48-50). Another proof for the activity of curcumin metabolites is the biological activity of curcumin treated with alkali, which is known to destabilize curcumin (51).

Many studies have shown that in multi-factorial diseases such as cancer, some agents that affect various cellular and molecular targets may be of higher therapeutic value (5, 30, 52). Among these agents, curcumin shows suitable properties and can affect different pathways in various diseases such as cancer (52, 53). Melanoma is known as one of the important malignancies that shows poor diagnosis and high resistance to different treatment regimens. Mounting evidence indicates that curcumin affects several molecular and cellular pathways involved in melanoma pathogenesis such as MST1, JNK, Foxo3, Bim-1, Mcl-1, BCl-2, Bax and JAK-2 / STAT-3 (54-56) making it a promising therapeutic agent to be used against this type of cancer. Figure 1 shows various cellular and molecular pathways influenced by curcumin in melanoma.

In a research, Bush et al. investigated the molecular pathways targeted by curcumin during apoptosis in human melanoma cells (56). They revealed that curcumin can induce cell death in various melanoma cell lines with wild-type or mutant p53. They also showed that curcumin induces apoptosis dose- and time-dependently in melanoma cell lines. Their results indicated that curcumin induced cell death via different pathways e.g. activation of caspases-3 and caspases-8 but not caspase-9 via a membrane-mediated mechanism. In addition, it was shown that curcumin could induce Fas receptor aggregation in a FasL-independent manner (56). Previous studies showed that suppression of receptor aggregation inhibited curcumin-induced cell death. Some

evidence revealed that melanoma cells with mutant p53 show strong resistance to conventional chemo-therapeutic agents (56).Therefore, curcumin might be able to overcome the chemo-resistance of these cells and open new horizons in cancer therapy.

Zhang et al. investigated the effects of curcumin on the migration, proliferation and invasiveness of human melanoma cells (57). In the referred study, A375 cells were cultured, passaged and treated with different concentrations of curcumin. Different concentrations of curcumin induced significant changes in the morphology of A375 cells. The results indicated that curcumin can significantly inhibit the migration and invasion of A375 cells compared with the control group. Curcumin (50, 25 and 12.5 mM) significantly decreased the number of A375 cells in the treated group. In addition, the rates of apoptosis at the concentrations of 6.25 and 12.5 mM of curcumin were significantly higher than those of the control group. On the other hand, phosphorylation levels of STAT-3 and JAK-2 at the concentrations of 10 and 20 mM of curcumin were significantly lower than those in the control group. Bcl-2 protein expression at the concentrations of 1, 2.5, 5, 10, and 20 mM of curcumin was significantly lower compared with the control group. In this latter study, curcumin showed various effects such as anti-proliferative and pro-apoptotic activities on A375 cells, and the inhibition of JAK-2/STAT-3 signaling pathway was suggested as one of mechanisms through which curcumin exerts its effects on this cell line (57).

Philip et al. showed that osteopontin (OPN) induces nuclear factor kappa B (NF-κB) through pro-matrix metalloproteinase 2 activation via IkappaB alpha/IKK signaling pathways which are down-regulated by curcumin in a melanoma mouse model (58). Their results indicated that curcumin could inhibit NF-κBB-DNA binding, NF-κB transcriptional activity and the OPN-induced translocation of p65. The authors revealed that curcumin could inhibit OPN-induced cell

migration, extracellular matrix invasion, and cell proliferation. Also, curcumin can synergistically induce apoptotic morphological changes by OPN in melanoma cells. Moreover, curcumin suppresses OPN-induced tumor growth in nude mice, and inhibits the activation of OPN-induced tumor and the levels of pro-MMP-2 expression. Table 1 illustrates the effect of curcumin on melanoma reported by different studies (58).

An important mediator of the cell stress response is heat shock protein 90 (Hsp90), which has been reported to be up-regulated in melanoma (59), and its inhibition, along with the inhibition of Hsp70, has been reported to enhance the sensitivity of melanoma cells to the anti-tumor effects of hyperthermia (60). Interestingly, there is evidence showing that curcumin synergistically enhances the anti-tumor effect of bortezomib in melanoma through inhibition of Hsp90 expression (61). Hemeoxygenase/biliverdin reductase (HO/BVR) is another main component of the cell stress response (62, 63). This system facilitates the degradation of heme which is toxic if produced in excess or unbalanced under redox conditions (64). Recently, it was found that HO/BVR system is up-regulated in melanoma patients (65). Interestingly, among the pharmacological effects of curcumin, enhancement of the cell stress response was mediated through HO/BVR (66). Hence, regulation of cell stress response could be regarded as a potential mechanism curcumin may affect development and progression of melanoma.

Parallel to the identification of many anti-cancer effects of curcumin, some studies have indicated that this agent could cause potential adverse effects under specific conditions (67, 68). There is some data showing that curcumin could induce chromosomal alterations and DNA damage, both *in vitro* and *in vivo* (69). However, Kurien and colleagues indicated that curcumin does not bind or intercalate into DNA (70). It should be noted that this binding could be caused by the solvent of curcumin (e.g. organic solvents) rather than the compound itself (70). Inhibition

of several drug-metabolizing enzymes including CYP3A4, glutathione-S-transferase and UDP and UDP-glucuronyl transferase is another effect of curcumin which may induce potential drug interactions (71). Although such sporadic reports on the potential adverse effects of curcumin exist and necessitate further evaluations, the trend in findings is in favor of the acceptable safety of this compound. Moreover, conducted clinical trials of curcumin have shown the safety of curcumin for human use, even in studies administering highly bioavailable preparations of curcumin. It is also interesting to note that curcumin has been affirmed with a GRAS (generally recognized as safe) status by the US Food and Drug Administration.

Table 1. Effects of curcumin on melanoma as reported by various studies.

Dose	Target gene	Effects	Model (in vitro/ in vivo/human)	Type of cell line	Ref
0-80 mM	mPTP	Facilitating mPTP death pathway	*In vitro*	WM-115, B16	(72)
10, 20 mM	JAK-2 / STAT-3	Anti-proliferative and pro-apoptotic activities	*In vitro*	A375	(57)
10 μM	-	Inhibition of proliferation and stimulation of	*In vitro*	B16F10	(73)

		differentiation			
15 μM	Mcl-1, Bcl-2, Bax, caspase-8, Caspase-3, NF-κB, p38, p53	Apoptosis induction	*In vitro*	A375, MV3 , M14	(74)
30-40 μM	caspase-3/7	Apoptosis induction	*In vitro*	B16F10	(75)
10 μM	ERK /Akt	Apoptosis induction	*In vitro*	A375	(76)
30–100 μM	mPTP, ANT-1	Apoptosis induction	*In vitro*	WM-115	(77)
0.2-5 μg/ml	caspases 8, 9 , 3	Apoptosis induction	*In vitro*	G-361 , A375	(78)
25 μm/ml	MST1, JNK, Foxo3 , Bim-1	Apoptosis induction	*In vitro*	B16 and WM-115	(79)
2.5 mM	MRP1, GSTM1	Apoptosis induction	*In vitro*	CAL1	(80)
< 5 μM	-	Decreasing cell growth	*In vitro*	B16-F10	(81)
50 μM	-	Inhibition of tumorigenesis and angiogenesis	*In vitro, in vivo*	B16F1 , B16F10, A375 ,	(82)

				SK-Mel-28	
10^{-5} M	PDE1A	Anti-proliferative effect	*In vitro*	B16F10	(83)
20 μM	-	Inhibition of melanogenesis	*In vitro*	B16F10	(84)
50 μM	NFκB, MT1-MMP, MMP-2	Inhibition of tumor growth and decrease migration	*In vitro, in vivo*	B16F10	(85)
1.25–10 μM	PI3K/Akt/ GSK 3β, ERK , p38 MAPK	Inhibits melanogenesis	*In vitro*	B16	(86)
High dose	-	Apoptosis induction	*In vitro*	G361, A375	(87)
100 mg/kg	EphA2, PI3K, MMP-2, MMP9	Inhibition of tumor growth and vasculogenic mimicry	*In vitro*	B16F10	(88)
10 μM	Caspase 3 , Caspase 9, Bcl-XL , X-IA	Induce apoptosis	*In vitro*	B16 , WM-115	(89)

10 μM	MITF, MEK/ERK , PI3K/Akt	Suppressive activity on α-MSH-stimulated melanogenesis	*In vitro*	B16F10	(90)
10-30 μM	caspase-9 , caspase-3	Induce apoptosis	*In vitro*	M21 , SP6.5	(55)
20 μM	PRL-3	Inhibition of metastasis	*In vitro, in vivo*	B16 , B16BL6	(91)
20 μM	STAT1 , STAT5, IFN-alpha, IFN-gamma, interleukin-2	Apoptosis induction	*In vitro*	A375 , Hs294T	(92)
50 μM	Akt, NF-kB, Bcl_{XL}, Erk,VEGF, cyclin D1	Blocks tumor formation	*In vitro, in vivo*	B16F10	(93)
-	bcl-2, P53	Apoptosis induction	*in vivo*	B16	(94)
75 μM	eIF2α, GADD 153, aspases-3 /7, Bcl-2	Apoptosis induction	*In vitro*	B16F10	(95)
50 μM	COX-2, cyclin D1, NF-kB	Apoptosis induction	*in vivo*	B16F10	(96)

30 μM	c-myc , caspase-3	Apoptosis induction	*In vitro*	A375	(97)
6.1-7.7 μM	NF-kB, IKK	Antiproliferative and apoptotic	*In vitro*	C32, G-361, , WM 266-	(54)
30 μM	GSTP1, MRP1	Inhibition of the multidrug resistance	*In vitro*	A375	(98)
18, 27 μM	-	Inhibition of growth of B16-R melanoma	*In vitro, in vivo*	B16-R	(99)
15 μM	MMP-2	Anti-metastatic	*In vitro*	B16F10	(100)
50 μM	iNOS, NF-kB	Apoptosis and cell cycle arrest	*In vitro*	A375	(101)
2.6 , 1.9 μM	GST	Inhibition of the multidrug resistance	*In vitro*	CAL1	(102)

dependent manner	Nm23, E-cadherin	Anti-metastatic properties	*In vitro, in vivo*	B16F10	(103)
50 , 100 µM	OPN, NF-kB	Apoptosis induction	*In vitro, in vivo*	B16F10	(58)
30 µM	aspases-3/8	Apoptosis induction	*In vitro*	MMAN, MMRU, RPEP, ,PMWK, Sk-mel-2, Sk-mel-5, , Sk-mel-28 c, MEWO	(56)
125 µg/ml	COX-I, COX-II	Antioxidant and anti-inflammatory activities	*In vitro*	SKMEL-28, M14, , UACC-62	(104)
25 µM	GST	Inhibition of the multidrug	*in vivo*	IGR-39	(105)

		resistance			
200 nmol/kg	-	Inhibition of lung metastasis	*in vivo*	B16F10	(106)

Curcumin analogs as powerful tools in melanoma therapy

Mounting evidence indicates that curcumin has multiple biological effects that make it a promising therapeutic candidate to be used in the treatment of several diseases such as cancer (107). On the other hand, it was observed that this agent has low oral bioavailability which led to the development of curcumin analogues (such as DM-1, EF24, D6 and CDF) with better anti-cancer effects and bioavailability (52). DM-1, one of the curcumin analogues, has shown anti-tumor effects in various *in vitro* and *in vivo* models (107, 108). It has been confirmed that this compound is not only a suitable anti-cancer agent with anti-metastatic and anti-proliferative activities but also it has minimal side effects on normal cells (109, 110). Table 2 shows various curcumin analogues that can be used in melanoma therapy.

Commercial curcuminoids include curcumin, demethoxycurcumin and bisdemethoxycurcumin. Most of the studies assessing the effects of curcumin against melanoma have been conducted with curcumin. Therefore, the impact of demethoxy and bisdemethoxy analogues, which are known to differ with curcumin in some properties (111), in reducing the progression of melanoma remains to be clarified. Four major strategies that could be used to improve the pharmacokinetic profile and enhance the delivery of curcumin are (1) Liposomes, micelles, and

phospholipid complexes; (2) Glucuronidation/metabolism interference via co-administration of curcumin with adjuvants like piperine; (3) Nanoparticles; and (4) Emulsifying or dispersing agents. Below, some of the studies on these forms of curcumin in melanoma are summarized.

In a study, Lo et al. reported that two compounds namely, 1,7-bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one (BHPHTO) and bisdemethoxycurcumin (BDMC) can inhibit the proliferation of melanoma cells (112). Moreover, Faião-Flores et al. revealed that curcumin analogue DM-1, alone or in combination with dacarbazine (DTIC), shows anti-tumor effects as it inhibited melanoma progression in a melanoma mouse model (113). In addition, no toxicological changes were observed in organs such as the spleen, kidneys, liver and lungs after the administration of DM-1, either alone or in combination with DTIC. DM-1 in combination with DTIC improved the recovery from anemia induced by melanoma and immunomodulation. It was found that DM-1 alone and in combination with DTIC induces apoptosis via the cleavage of caspase-8, -3 and -9. These results indicated that DM-1 shows therapeutic effects on melanoma via a preferential intrinsic apoptotic pathway by decreasing Bcl-2/Bax ratio (113).

In another study, Pisano et al. indicated that D6, a curcumin analogue, has anti-tumor activity against melanoma and neuroblastoma cells (114). This study revealed that α,β-unsaturated ketone D6 shows stronger therapeutic effects in inhibiting melanoma growth in comparison with curcumin. Various experiments were done in this study such as clonogenic assay, TUNEL assay, annexin-V staining and caspases activation assay, and PARP cleavage assay. These experiments confirmed that D6 is more effective in the treatment of melanoma and neuroblastoma when compared with curcumin. Hence, this data suggested that D6 can be considered as a good candidate for new therapies against neural crest-derived tumors (114).

Dahmke et al. reported that "deketene curcumin" shows better therapeutic effects than curcumin on melanoma cells (115). This form of curcumin could induce toxicity in B78H1 melanoma cells that finally leads to G2 arrest. Their results confirmed that deketene curcumin can be used as an anti-cancer agent that possesses better bioavailability than curcumin (115).

Novel therapeutic approaches for curcumin targeting in melanoma

Various studies on bio-distribution, absorption, elimination, and metabolism of curcumin have indicated that this agent has rapid metabolism, poor absorption and rapid elimination from the body. Therefore, low systemic bioavailability of oral curcumin is known as a major limitation of its use (128). However, it should be considered that many of the metabolites and degradation products of curcumin, possess strong biological and pharmacological activities (48-50).

Several studies utilized different approaches to overcome the aforementioned limitations. Using adjuvants can be a suitable approach to block curcumin metabolic pathways and improve its bioavailability (129). Various delivery systems such as liposomes, nanoparticles, micelles, and phospholipid complexes have been proposed to improve the pharmacokinetic properties of curcumin for cancer therapy. For example, micelles and phospholipid complexes can improve the gastrointestinal absorption of curcumin which results in higher plasma levels (129). Another strategy is to enhance the aqueous solubility of curcumin. Recently, Kurien et al. reported enhancement of the solubility of curcumin in water by 35 folds by heat under pressure. Interestingly, heat-solubilized curcumin was shown to increase pharmacological effect of curcumin in mice with systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS) (130). This finding is in line with previous studies showing enhanced solubility and biological activity

of heat-treated curcumin (131-133). Table 3 illustrates novel curcumin delivery systems used in melanoma therapy.

In a study, Lu et al. showed that curcumin micelles remodel tumor microenvironment and enhance vaccination efficacy in a model of advanced melanoma. In this study, an amphiphilic curcumin-based micelle (curcumin-PEG conjugate; CUR-PEG) was intravenously administered to a mouse model of melanoma (30). Their results indicated that CUR-PEG and vaccine treatments have a stronger anti-tumor effect compared with separate treatments. Their study showed that utilization of combination therapy leads to significant IFN-γ production (7-fold increase) and cytotoxic T cell response (41.0±5.0% specific killing). Moreover, in the tumor microenvironment, these therapies led to significantly down-regulated levels of immunosuppressive factors including myeloid-derived suppressor cells (*MDSCs*), T-reg cells and IL-6, while increased $CD8^+$ T cell population. It has been observed that some pro-inflammatory cytokines such as TNF-α and IFN-γ have different expressions in the tumor microenvironment. the aforementioned combination therapies could switch macrophage polarization to M1 phenotype and down-regulate the STAT3 pathway in the treated tumors. It was found that CUR-PEG can improve the effects of immunotherapy in melanoma. Novel generations of drug delivery systems such as nanoparticle (NP) technology have provided promising solutions to improve the bioavailability of therapeutic agents. This delivery system will probably be suitable for hydrophobic agents like curcumin that have low aqueous solubility (30).

In another study, the effect of dipeptide nanoparticles of curcumin on melanoma was evaluated (134). A non-protein amino acid, α, β-dehydro-phenylalanine, was used to entrap curcumin in the dipeptide NPs, and the anti-tumor effects of dipeptide-curcumin NPs were assessed in cancer models *in vitro* and *in vivo*. Using different dehydro-dipeptides, it was found that methionine-

dehydro-phenylalanine can be regarded as a suitable dehydro-dipeptide for loading and releasing curcumin. In the mentioned study, it was revealed that loading curcumin in dipeptide NPs can improve its cellular availability and solubility, increase its toxicity in various cancer cell lines, and improve curcumin's efficacy in inhibiting tumor growth in mice bearing melanoma tumor. Curcumin-dipeptide NPs also showed enhanced *in vitro* and *in vivo* chemotherapeutic effects compared with free unformulated curcumin . These delivery systems have several advantages as they are highly biocompatible and easy to make, and possess a suitable capacity of loading and releasing curcumin. Moreover, curcumin's cellular uptake is improved with dipeptide NPs (134).

In another study, Loch-Neckel et al. examined the effect of orally administered chitosan-coated polycaprolactone NPs containing curcumin on metastatic melanoma in the lungs (36). Their results indicated that curcumin could decrease cell viability and induce apoptosis in B16F10 melanoma cells. They found that curcumin significantly reduces the expression of metalloproteinases in melanoma cells. Several studies showed that metalloproteinases are associated with the proliferation and migration of melanoma cells. The utilization of chitosan-coated NPs containing curcumin decreased pulmonary tumor formation in a melanoma lung metastasis model. In addition, histological analyses indicated a few small nodules of melanoma in lungs of mice treated with this system. Hence, curcumin-containing chitosan-coated polycaprolactone NPs may be a suitable system for the treatment of malignant melanoma (36).

Table 2. Various curcumin analogs in melanoma therapy

Type of curcumin	**Dose**	**Target gene**	**Model (*in vitro*/ *in vivo*/human)**	**Type of cell line**	**Ref**

Tetrahydrocurcumin	dependent manner	-	*In vitro*, *in vivo*	B16F-10	(116)
Salicyl curcumin	dependent manner	-	*In vitro*, *in vivo*	B16F-10	(116)
Curcumin III	dependent manner	-	*In vitro*, *in vivo*	B16F-10	(116)
D6	17.5 mg/kg	Caspase-3 and 7	*In vitro*, *in vivo*	LB24, CN-MelA, GR-Mel , WM266-4 , 13443, M14	(114)
Curcumin ferrocenyl derivatives	17.9 μM	-	*In vitro*	B16	(117)
(2E,6E)-2,6-bis(2,5-Dimethoxybenzylidene) cyclohexanone	50 μM	tyrosinase,	*In vitro*	B16	(118)

Curcumin- 13c	20 μM	FGF-R1, EGFR, Btk, Mink, Ret , Itk	*In vitro, in vivo*	B16F10	(119)
Curcumin- compound **C5**	0.71 μg/mL	tubulin polymerization inhibitory	*In vitro*	B16-F10	(120)
DM-1	5 μM	TNF-R1 , caspase 8	*In vitro, in vivo*	B16F10, A375	(113)
DM-1	75 μM	Mcl-1 , Bcl-xL	*In vitro*	SK-MEL-5 and A375	(121)
FLLL32/62	2 μM or 4 μM	STAT3	*In vitro*	A375 , HT144 Hs294T	(122, 123)
D6	270 nM	p53, PI3K/Akt , NF-kB	*In vitro, in vivo*	LB24Dagi	(124)
Gercumin II	250 μM	-	*In vitro*	SK-	(125)

				MEL-28	
Bisdemethoxycurcumin (BDMC)	25-100 μM	-	*In vitro*	A2058, B16-F10	(112)
Deketene curcumin	20 μM	G2 arrest	*In vitro*	B78H1	(115)
curcumin-biphenyl derivatives	1 , 10 μM	-	*In vitro*	WM266, CN, LB24Dagi, PNP	(126)
DM-1	83 μM	caspase-3, -8 and -9	*In vitro, in vivo*	B16F10	(35)
NC 2067	2.0–2.4 μM	-	*In vitro*	A375	(127)

Table 3. Novel curcumin delivery systems in melanoma therapy

Type of curcumin	**Dose**	**Target gene**	**Model (*in vitro*/ *in vivo*/human)**	**Type of cell line**	**Ref**
Curcuminbased micelle	-	IL-6 , CCL2, TNF-α , IFN-γ	*In vitro, in vivo*	B16F10	(30)
Curcumin -FAPαc -CpG		indolamine-2,3-dioxygenase	*In vitro, in vivo*	B16	(53)

Curcumin- RGD-PEG-PLA	-	-	*In vitro*	B16	(52)
Chitosan-coatedliposomes-containing **curcumin**	2.5 μM	-	*In vitro*	B16F10	(135)
Curcumin – ANPs					(136)
methionine-dehydro-phenylalanine-curcumin NPs	30 μM	-	*In vitro, in vivo*	B6F10	(134)
Curcumin-RGD-lpNPs	25 mg/kg	-	*In vitro, in vivo*	B16	(137)
curcumin-loaded SPC liposomes	20 $mg \cdot kg^{-1}$	-	*In vitro*	B16-F10	(138)
Curcumin- MBCSPs	500 μg ml^{-1}	-	*In vitro, in vivo*	B16F10	(139)
Curcumin- β-Cyclodextrin	14 μM	-	*In vitro*	A375	(140)
Curcumin- β-Cyclodextrin-gemini	14 μM	-	*In vitro*	A375	(140)

surfactant					
chitosan-coated nanoparticles containing curcumin	100 mM	MMP-2, MMP-9	*In vitro, in vivo*	B16F10	(36)
Curcumin/magnetite nanoparticles	66.0 μM	-	*In vitro*	B16-F10	(141)
Curcumin - chitin nanogels	0.1-1.0 mg mL^{-1}	-	*In vitro*	A375	(142)
Curcumin- HP-β-CD	300 μg/ml	G2/M stage	*In vitro*	B16-F10	(143)
Curcumin- PEO-PCL	10 , 80 μM	-	*In vitro, in vivo*	B16F10	(144)
Curcumin- Muc18	167–335 nM	NF-kB	*In vitro, in vivo*	B16F10	(145)
curcumin plus PDMP	10 μM	PI3K/AKT	*In vitro*	WM-115 and B16	(146)
curcumin-nano-capsules	6 mg/kg	-	*In vitro, in vivo*	B16-F10	(147)
EF-24-FFRmk-fVIIa	1.5 μM	-	*In vitro*	RPMI-7951	(148)
Curcumin - XGO-b-PCL	1–100 μM	-	*In vitro*	B16F10	(149)

FAP: fibroblast activation protein; PEG-PLA: polyethylene glycol-polylactic acid ; ANPs: albumin

nanoparticles; NP: nanoparticle; SPC: soybean phosphatidylcholine; MBCSPs: magnetic-based core-shell particles; HP-β-CD: hydroxypropyl-β-cyclodextrin; PEO-PCL: poly(ethylene oxide)-b-poly(epsilon-caprolactone); PDMP: 1-phenyl-2-decanoylamino-3-morpholino-1-propanol; FFRmk-fVIIa: EF-24-phenylalanine-phenylalanine argininechloromethyl ketone-factor VIIa; XGO-b-PCL: xyloglucan-block-poly(ϵ-caprolactone).

Curcumin and microRNAs in melanoma

MicroRNAs (miRNAs) are known as small and noncoding RNAs that can suppress gene expression at post-transcriptional levels via sequence-specific interactions with the 3'-untranslated regions (UTRs) of cognate mRNA targets (150, 151). In addition, miRNAs are involved in the regulation of various key cellular processes such as apoptosis, proliferation, differentiation, and development (151-154). Alterations in miRNA expression have been observed in a number of cancers, including melanoma. These alterations can arise from either genetic or epigenetic changes (155). It has been suggested that dietary components may modulate miRNA expression (156). Few studies have investigated the effect of curcumin on the expression of miRNAs in melanoma. Table 4 illustrates various miRNAs affected by curcumin in different cancers.

Dahmke et al. revealed that curcumin intake can affect miRNAs in murine melanoma. They indicated that miR-205-5p was the most significantly altered miRNA (38). This latter study showed that oral administration of curcumin can influence the miRNA signature of engrafting melanoma. Dahmke et al. evaluated the effects of curcumin in a melanoma model, which was established by the injection of murine B78H1 cells in the flank of C57BL/6 mice. Curcumin-containing diet (4%) was administered two weeks prior to the injection of tumor cells until the end of the experiment. The results indicated that curcumin feeding significantly decreases the

growth of the flank tumors and substantially alters miRNA expression signature in tumors. For example, miR-205-5p was expressed over 100 times higher in the treatment groups compared with the control group. MiRNAs can have various targets in melanoma cells. Western blot analyses indicated that some targets such as proliferating cell nuclear antigen (PCNA) and anti-apoptotic B-cell CLL/lymphoma 2 (Bcl-2) were significantly down-regulated in the treatment groups. This study proposed that there are alterations in the miRNA expression in engrafting curcumin-treated melanoma and miR-205-5p was the most significantly altered miRNA (38).

Diphenyldifluoroketone (EF24) is known as a curcumin analogue with anti-tumor effects that are mediated via inducing apoptosis and arresting cell cycle. Zhang et al. investigated the effect of EF24 on miR-33b in melanoma cells (157). They revealed that at non-cytotoxic concentrations, EF24 is able to suppress epithelial-to-mesenchymal transition (EMT) and cell motility of melanoma cell lines such as A375 and Lu1205. In addition, EF24 suppressed HMGA2 expression at mRNA and protein levels. MiR-33b can directly bind to 3' untranslated region (3'-UTR) of HMGA2 and suppress its expression. It was shown that miR-33b inhibition or HMGA2 over-expression reverts EF24-mediated suppression of EMT. Moreover, EF24 modulates the focal adhesion assembly, Src, FAK and RhoA activation, and HMGA2-dependent actin stress fiber formation via targeting miR-33b. Hence, these results propose that EF24 can suppress melanoma metastasis by up-regulating miR-33b and concomitantly decreasing HMGA2 expression (157).

Yang et al. confirmed that EF24 targets NF-κB and miRNA-21, and possesses a promising anti-tumor activity (39). EF24 has been reported to inhibit the NF-κB pathway in DU145 human prostate cancer cells and B16 murine melanoma cells. Moreover, EF24 induced apoptosis in these cells apparently via inhibiting miR-21 expression, and also improved the expression of

several miR-21 target genes, e.g. PDCD4 and PTEN. This molecule inhibited miR-21 expression and lung metastasis, prolonged animal survival and increased the expression of miR-21 target genes in a mouse model of melanoma. Moreover, EF24 enhanced the expression of potential tumor suppressor miRNAs and inhibited the expression of oncogenic miRNAs, such as miR-21. These findings proposed that EF24 shows anti-cancer activities via regulating NF-κB pathway and miRNA expression (39).

Table 4. MiRNAs affected by curcumin in various cancers

MiRNA	**Type of curcumin**	**Cancer**	**Expression in cancer**	**Target gene**	**Model**	**Type of cell line**	**Ref**
miR-33b	EF24	Melanoma	Up - regulation	E-cadheri, STAT3	*In vitro*	Lu1205 and A375	(157)
miR-205-5p	Curcumin	Melanoma	Up-regulation	Bcl-2, PCNA	*In vitro, In vivo*	B78H1	(38)
miR-21	EF24	Melanoma	Down-regulation	NF-κB, JAK-STAT, PTEN , PDCD4	*In vitro, In vivo*	B16	(39)
miR-34a	Curcumin	colorectal	Up regulation	-	*In vitro*	HCT116, RKO, SW480,	(158)

						SW620, HT29, Caco2	
miR-27a	Curcumin	colorectal	Up regulation	-	*In vitro*	HCT116, RKO, SW480, SW620, HT29, Caco2	(158)
miR-7/ let-7a, b, c, d, miR-26a, miR-101, miR-146a, miR-200b, c	Curcumin/diflourinated-curcumin	pancreatic	Up regulation	EZH2, Notch-1, CD44, EpCAM	*In vitro*	AsPC-1 , BxPC-3/ AsPC-1 and MiaPaCa-2	(159, 160)
miR-192-5p/215	Curcumin	lung	Up regulation	P53	*In vitro, In vitro*	H460 , A427	(161)

miRNA-186*	Curcumin	lung	Down regulation	caspase-10	*In vitro*	A549	(162)
miR-125a-5p	Curcumin	nasopharyngeal carcinoma	Down regulation	TP53	*In vitro*	HONE1	(163)
miR-9	Curcumin	ovarian	Up regulation	Akt/FOXO1	*In vitro*	SKOV3	(164)
miR-205	PLGA-CUR NPs	Prostate	Up regulation	STAT3 , AKT , Mcl-1, Bcl-xL	*In vivo*	LNCaP	(165)
miR-19	Curcumin	Breast cancer	Up regulation	PTEN, p-AKT, p-MDM2, p53	*In vitro*	MCF-7	(166)
miR-200a/b	Curcumin	Hepatocellular carcinoma	Up regulation	Bcl-2, Bad	*In vitro*	HepG2 , HepJ5	(167)
miR-15a/16-1	Curcumin	Leukemia	Up regulation	WT1	*In vitro*	K562 , HL-60	(168)
miR-203	Curcumin	Bladder	Up regulation	Akt2 , Src	*In vitro*	T24, J82 and TCCSUP	

PLGA-CUR NPs: poly (lactic-co-glycolic acid)-curcumin-nanoparticles.

Conclusion

Melanoma, a malignant tumor of melanocytes, is one of the most aggressive types of malignancies. Although melanoma comprises less than 5% of all skin cancers, it is responsible for the majority of skin cancer-related deaths. At early stages, melanoma can be treated by surgical resection; however, most often it progresses to the invasive stage and does not respond to conventional treatments largely due to the development of multi-drug resistance. Hence, new therapies are required to overcome the limitations of conventional therapies. Several lines of evidence have indicated that curcumin affects key pathways that are involved in different cancers such as melanoma. It seems that this molecule plays an important role in cancer therapy. Several targets at the cellular and molecular levels (e.g. signaling pathways, transcription factors and miRNAs) are affected by curcumin in melanoma. Hence, curcumin can be regarded as a promising agent in the treatment of melanoma. Nevertheless, utilization of curcumin is associated with some limitations such as rapid metabolism, low oral absorption and rapid elimination from the body. These limitations may attenuate efficacy and decrease the therapeutic effects of curcumin. New formulations and novel delivery systems have opened a new window into the landscape of treatment of various diseases such as melanoma with curcumin. Finally, most of the evidence on the efficacy of curcumin against melanoma and other types of cancer pertains to pre-clinical studies. Although some clinical evidence exists that favors the benefits of curcumin supplementation in cancer patients (169-171), clinical evidence is still scarce and a thorough outcome study is yet to be performed. Hence, clinical proof-of-concept investigations are required to verify the translational value of the reported anti-tumor effects of curcumin in animal and cellular models of cancer. However, further evidence from prospective clinical trials is required to decipher the place of curcumin in the clinical management of melanoma.

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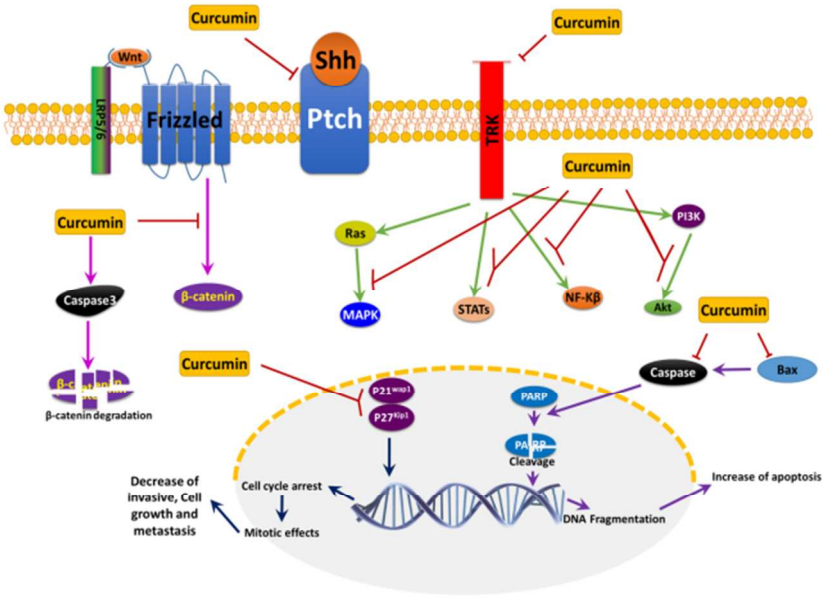

Figure 1. Cellular and molecular pathways affected by curcumin in melanoma. MAPK: mitogenactivated protein kinase; STAT: signal transducer and activator of transcription; NF-Kb: nuclear factor kappa-light-chain-enhancer of activated B cells; PARP: poly(ADP-ribose) polymerase
206x126mm (300 x 300 DPI)