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Role of phytoconstituents and extract against melanoma

Numerous plant extracts and phytoconstituents have been well exploited for melanoma therapy for their ability to suppress melanoma through the regulation of oxidative status, modulation of immunity, correction of disordered replication and induction of apoptosis, prevention of invasion, angiogenesis, and metastasis.[1,2] Multiple mechanisms are involved in the development, progression, invasion, angiogenesis, and metastasis of melanoma. Hence, it is rational to use plant extract or fraction (comprising numerous phytoconstituents) that may act synergistically in a multi-targeting manner rather than a single constituent or drug molecule. A comprehensive list of plant extracts and their bioactive phytomolecules are demonstrated in supplementary Table S1.

Table S1 Studies on plants and their constituents for melanoma therapy.

Plant species	Anticancer activity and the reported mechanism	References
Ephedra sinica	Antiangiogenic and antiinvasive activities against B16-F10	3
Azadirachta indica (aqueous extract of leaves)	Cytotoxicity against B16 melanoma • no direct cytotoxic effect on B16Mel cells • extract activated spleen cells are cytotoxic to tumor cells *in vitro* • Immune activation (lymphocytosis: increase in CD4+ and CD8+ T cells) Anticancer activity in C57BL/6 mice: insignificant difference in tumor growth as compared to that of tumor control, however extract activated spleen cells are cytotoxic to tumor cells *in vivo* (co-culture containing spleen cells + B16 cells while used for syngenic tumor model) • ↓ tumor volume • ↑ life span	4
Azadirachta indica (aqueous extract of leaves)	• Enhance the efficacy of poorly immunogenic B16 melanoma surface antigen vaccine (B16MelSAg) • Vaccination of C57BL/6 mice with B16MelSAg+extract more efficiently prevented the growth of B16 melanoma tumor	5
Nimbolide	Antiproliferative activity against B16 cell lines	6
Aerial and root parts and seed oil of *Eruca sativa* extracted with petroleum ether, ethyl acetate, and methanol	Inhibited the cell proliferation of B16F10 Anticancer activity in C57BL/6J mice: ↓ tumor volume and weight Seed oil significantly reduced the tumor growth Inhibited angiogenesis in mice	7
Eruca sativa seed oil	Anticancer activity in C57BL/6J mice: ↓ tumor volume	8
Tinospora cordifolia (70% methanolic extract)	Antiangiogenic activity in *in-vitro* and *in-vivo* (C57BL/6 mice) • ↓ microvessel outgrowth from the rat aorta • ↓ the number of tumour directed capillaries formation), ↓ proinflammatory cytokines (IL-1β, IL-6, TNF-a,	9

	granulocyte monocyte-colony stimulating factor (GM-CSF)) • ↓ vascular endothelial cell growth factor (VEGF) • Modulation of the immune system (Enhancement of immunopotentiating cytokines: IL-2 ((T-cell growth factor)) and TIMP-1 (Tissue Inhibitor of Metalloprotease-1)	
Polysaccharide from *Tinospora cordifolia*	Inhibition of lungs metastasis in C57BL/6 mice • ↓ lung collagen hydroxyproline, hexosamines, and uronic, acids that are markers of neoplastic development • ↓ serum gamma glutamyltranspeptidase	[10]
Aqueous Extract of *Tinospora Cordifolia* stems	• Immunomodulatory activity • Boosting the phagocytic ability of macrophages	[11]
Cordyceps militaris	• ↓ tumor growth via induction of apoptotic cell death in MeWo (HTB-65) • ↓ the production of VEGF through downregulation of Akt1 and GSK 3α/3β • ↑ p38α phosphorylation levels Anticancer activity in xenografted Balb/c nude mouse model • ↓ tumor volume • Massive necrotic/degenerative lesions inside the tumors, • Down-regulation of VEGF expression • Antiangiogenic activity	[12]
Viscum album tinctures	Cytotoxicity against B16F10 cells DNA fragmentation and apoptotic anatomy of cells Increased expression of early and late apoptotic markers on tumoral cells ↓G1, and an ↑ S or G2/M populations	[13]
Viscum album extract	Inhibition of lungs metastasis in C57BL/6 mice: Inhibit lung nodule formation ↓ lung hydroxyproline and serum sialic acid levels ↑ life span	[14]
Viscum album	Anticancer activity in C57BL/6N mice Upregulation of pro apoptotic genes (Trp53bp2, Nol3, Fadd, Tnfsf10, Traf1, Traf2, Cflar, Card10, Nod1, Casp 2, Casp7, Xiap, Dad1, and Dffb)	
Calendula officinalis flower ethanolic extract	• Inhibition of lungs metastasis in C57BL/6 mice • ↓ lung metastatic tumor nodules • ↑ life span. • ↓serum hydroxyproline, uronic acid, hexosamine, serum sialic acid, GGT • Inhibition of expression of MMP-2 and MMP-9 • Activation of TIMP-1 and TIMP-2 • ↓proinflammatory cytolines ((IL-1β, IL-6, TNF-α, GM-CSF) • ↓ VEGF • ↑ IL-2	[15]
Ethyl acetate fraction of *Calendula officinalis* flowers	• ↓ α-MSH-induced melanin production • ↓ cell migration ability of melanoma cells • Inhibition of expression of MMP-2 via suppression of the mitogen-activated protein kinase (MAPK) signaling pathway.	[16]
Laser-activated Calendula aqueous extract	• Cell cycle arrest in G0/G1 phase • Caspase-3-induced apoptosis *in vivo* anti-tumor effect in solid tumor with nude mice bearing ANDO-2 human melanoma cell line. • Tumor growth inhibition	[17]

	• Prolong survival time	
70% hydroalcoholic extract of *Calendula officinalis* flowers	Cytotoxicity against B16F10 cells	[18]
Isolated compounds from flower of *Calendula officinalis*	Cytotoxicity against melanoma cell lines	[19]
Andrographis paniculata	Antiangiogenic activity Modulation of the immune system	
70% ethanolic extract of the whole plant (*Andrographis paniculata*) and andrographolide	Antiangiogenic activity in C57BL/6 mice • ↓ proinflammatory cytokines (IL-1β, IL-6, TNF-α and GM-CSF) • ↓ VEGF level and serum NO level • ↑ antiangiogenic factors such as TIMP-1 and IL-2 • ↓ tumor-directed capillary formation	[20]
Andrographolide	• ↓ cell proliferation (B16 cells) • ↓ clonogenicity • Cell cycle arrest at the G1/S transition • Induced cell apoptosis *in vitro* Anticancer activity in C57BL/6J mice: • Suppressed melanoma tumor growth • Promoted tumor apoptosis • ↓ tumor volume • The BrdU and CD34 staining showed inhibition of tumor cell proliferation and angiogenesis • ↑ number of apoptotic cells in the tumor tissues • Inactivation of TLR4/NF-κB signaling pathway • Inhibited the mRNA and protein expression of CXCR4 and Bcl-6 Inhibition of lungs metastasis in C57BL/6J mice: • ↓ number of lung metastatic foci • ↓ size of the micrometastatic foci	[21]
Andrographolide	• Inhibit proliferation of human malignant melanoma cells (C8161 and A375) • Induce G2/M cell-cycle arrest • Induced apoptosis (through activation of caspase-3) • Activates the JNK and p38 signaling pathway (↑ the expression of p-JNK, JNK, p-P38 and P38)	[22]
Andrographolide	• Antiproliferative activity against M14, UACC62, and A431 cell line • Cell-cycle arrest at G0/G1 phase through induction of cell-cycle inhibitory protein p27 and decreased expression of CDK4 • Immunostimulatory activity (increased proliferation of lymphocytes and production of interleukin-2) • Enhanced the production of TNF-α and CD marker expression, resulting in ↑ cytotoxic activity of lymphocytes against cancer cells Anticancer activity in C57BL/6 mice: Inhibited the growth of tumor (↓ tumor volume)	[23]
Andrographolide	• Cytotoxicity against B16F-10 • Cell shrinkage, DNA fragmentation, membrane blebbing, and the presence of apoptotic bodies • ↓ cells in G1-phase, S-phase, and G2/M phase • Inhibit NF-κB-mediated bcl-2 activation	[24]

	• ↑ the expression of p53, caspase-9, caspase-3, and Bax gene • ↓ expression of bcl-2 gene • Down regulation of GM-CSF and proinflammatory cytokines TNF-α, IL-1β, and IL-6 • Inhibit the nuclear translocation of NF-κB subunits such as p65, p50, and c-Rel • Inhibit the nuclear translocation of other transcription factors c-fos, ATF-2, and CREB-1	
Andrographis paniculata leaf hydroalcoholic extract	• Downregulation of HIF-1α and VEGF • Downregulation of p1, p300, CBP	[25]
Piper longum (70% ethanolic extract)	Antiangiogenic activity in C57BL/6 mice: • ↓ number of tumor-directed capillaries • ↓ proinflammatory cytokine and VEGF • Increases IL-2 and TIMP-2 • Decreased cell migration of VEGF-induced migration of endothelial cells • Modulation of the immune system	[26]
Piperine	• ↓ proinflammatory cytokines (IL-1β, IL-6, TNF-α, IL-12p40, and GM-CSF) in B16F10 cells • Inhibition of NF-kB, ATF2, c-Fos, CREB • Inhibit MMP (MMP2 & MMP9)	[27]
Piperine	Inhibition of lungs metastasis in C57BL/6 mice: • Suppress tumor cell growth • ↓ metastatic nodule formation • ↑ survival rate and ILS • ↓ sialic acid, GGT, HP, Uronic acid	[28]
Piperine	• ROS production at tumor site • Imbalance of calcium homeostasis • Loss of mitochondrial membrane potential, caspase activations, and DNA fragmentation • Cell cycle arrest at G1 • Increase in the ratio of Bax to Bcl-2 • Upregulate the expression of apoptosis-inducing factor (AIF) • Alterations in the expression of MAPK family proteins and PI3K–Akt survival signals • Disrupt NF-kB signaling • Reversed multi drug resistance (MDR) by reducing UVB-induced p-glycoprotein activity	[29]
Piperlongumine	• Induce apoptosis via reactive oxygen species-mediated disruption of mitochondria in human melanoma (A375, A875) and murine melanoma (B16F10)	[30]
Piperlonguminine	• Suppress melanogenesis	[31,32]
Glycyrrhiza glabra root methanol extracts	• Cytotoxicity against A375.S2 and WM 136.1A cells	[33]
Isoliquiritigenin	• Induces mitochondrial dysfunction and apoptosis by inhibiting mitoNEET protein in a ROS-dependent manner in A375	[34]

Isoliquiritigenin	• Growth inhibition and apoptosis induction on melanoma cells (A375, A2058) • Downregulation of MiR-301b • ↑ the protein level of C-PARP, Bax, C-caspase-3 and decreased the protein level of Bcl-2	[35]
Isoliquiritigenin	• Inhibits proliferation of B16F10 cells • Induces apoptosis via alleviating hypoxia and reducing glycolysis in B16F10 cells	[36]
Lawsonia inermis leaf aqueous extract	Anticancer activity in C57BL/6 mice: ↓ tumor volume ↑ life span ↑ tumour volume doubling time ↑ inhibition rate	[37]
Solanum lycopersicum fruit extract	Anticancer activity in C57BL/6 mice: ↓ tumor volume ↑ life span ↑ tumour volume doubling time ↑ inhibition rate	[38]
Bauhinia veriegata leaves (50 % methanolic extract)	↑ life span of C57BL/6 mice ↓ tumor volume	[39]
Flavanone from the stem of *Bauhinia variegata*	Cytotoxic activity against (MALME, SK-MEL-2, SK-MEL-28, SK-MEL-5, UACC-257, and UACC-62)	[40]
Hydro-methanolic extract of leaf, stem bark, and flower of *Bauhinia veriegata*	Anticancer activity in C57BL/6 mice: • ↓ tumor volume • ↑ tumor growth inhibition (% TGI) • ↑ volume doubling time (VDT) • ↑ life span time • A higher proportion of apoptotic and dysplastic cells	[41]
Volatile composition of *Mangifera indica* leaves	Cytotoxicity against UACC.62 (melanoma) cells	[42]
Stem bark *Mangifera indica* Methanol extract	Cytotoxicity against LOX IHVI, M14, MALME-3M, SK-MEL-2, SK-HEL-28, SK-MEL-5, UACC-257, and UACC-62 cell lines	[43]
Mangiferin	• Cytotoxicity against B16F10 • Inhibitory effects on bFGF-induced cellular migration of • B16F10 • Inhibits bFGF and VEGF-stimulated endothelial cell growth • Inhibits capillary growth and tube formation in the human placental blood vessel • Inhibits IL6, TNF, IFNG, KDR (VEGFR2), PLAU, MMP19, CCL2 and PGF gene • Inhibits angiogenesis, cell proliferation, cell motility (invasion,migration), and cell viability inhibition of calcium signaling, lipid metabolism, and inflammatory pathways (NFkB, HMGB1, NO) Anti-angiogenic activity in C57BL/6 mice • Inhibit B16F10 tumor cell-induced angiogenesis • Inhibits TNF-induced neovascularization *in vivo*	[44]
Homo-polysaccharide (PSM001)	• Cytotoxicity against B16F10 and A375 • Inhibition of colony formation ability of B16F10 and A375 cells • ↓ MMP-9 and MMP-2 expression in A375 cells • ↑ TIMP-1 and TIMP-2 expression	[45]

	• ↓ VEGF Lungs metastasis in C57BL/6 mice • Inhibit the formation of lung metastatic nodules	
Aqueous extract of *Withania somnifera* root	• ↓ cell viability of A375 • Morphology alteration of A375 cells • Apoptotic induction (apoptotic body and nuclear blebbing) • DNA fragmentation of A375 cells	[46]
Withaferin A (WFA)	• Induces apoptotic cell death of M14, Mel501, SK28, Lu1205, WM793 cells • Prooxidant potential (early ROS production and glutathione depletion) • Nuclear condensation and fragmentation, inter-nucleosomal DNA fragmentation • ↓ overexpressed Bcl-2 • ↓ Bcl-2/Bax and Bcl-2/Bim ratios	[47]
70% methanol extract of root & bioactive molecule Withanolide D	• Lungs metastasis in C57BL/6 mice • Inhibit the metastatic colony formation • ↑ the survival days • ↓ Lung collagen hydroxyproline, hexosamine, uronic acid, γ -glutamyl transpeptidase etc. • ↓ serum sialic acid • ↓tumour mass around alveoli and pleura. • ↓ massive tumour growth and fibrosis	[48]
Standardized *W. somnifera* root extract	• ↓ viability of B16F1 cells • Fragmention of DNA • Inhibitor against antiapoptotic proteins (BCL-2, BCL-XL, and MCL-1)	[49]
Withaferin A	Anticancer activity in C57BL mice: • Prolongation of mean survival time • ↓ tumor volume • ↑ tumor growth delay	[50]
Withaferin A	Anticancer activity in C57BL mice: • ↑ volume doubling time • ↑ growth delay • ↓ tumor volume	[51]
Ganoderma lucidum extract	Decrease the viability of B16-F10 cells Inhibit the release of IL-8, IL-6, MMP-2 and MMP-9 in cancer cells under pro-inflammatory condition ↓ cell migration	[52]
Cinnamomum cassia bark aqueous extract	• *In vitro* cytotoxicity against B16F10 and Clone M3 cells • Cell cycle arrest at S phase in B16F10 cells • Up-regulating pro-apoptotic molecules (Bad, Bim, Bax and Bak) • Inhibition of Bcl-2, BcL-xL and survivin • Inhibition of NFkB and AP1 • Increased level of active caspase-3 Anticancer activity in C57BL/6 mice: • ↓ tumor volume, tumor weight • ↑ life span • Reduce the level of NFkB and AP1 • ↑ DNA fragmentation • ↑ active caspase-3 Inhibition of angiogenesis	[53,54]

	• Inhibition of pro-angiogenic factors (EGF, VEGF-α, TGF-β, and FGF) in *in-vitro* and *in-vivo* models • ↑ anti-tumor activities of $CD8^+$ T cells • ↓ Cox-2 and HIF-1α expression Anticancer activity in C57BL/6 mice • ↓ in tumor volume • ↓ tumor weight	
Cinnamic Aldehyde	• ↓ proliferation of human metastatic melanoma cell lines • Induces apoptosis with procaspase-3 cleavage in A375 human melanoma cells • Anti-invasive effects of A375 • Induces oxidative stress response in human A375 (up-regulate HMOX1, SRXN1, TXNRD1) • Inhibits NFκB transcriptional activity and suppresses IL-8 in human melanoma cells • G1 cell cycle arrest • Potentiate tumor suppressor gene cyclin-dependent kinase inhibitor 1A (CDKN1A) Anticancer activity in SCID mouse xenograft model • Suppression of tumor growth • ↓ tumor weight • Downregulation of cellular proliferation marker proliferating cell nuclear antigen (PCNA)	[55]
Cinnamomum cassia bark fraction (methanol, hexane, ethyl acetate fraction) and compounds (trans-cinnamaldehyde, eugenol)	Cytotoxicity against SK-MEL-2	[56]
Inonotus obliquus aqueous extract	• Inhibited the growth of B16-F10 cells • Cell cycle arrest at G0/G1 phase • Induction of apoptosis • Reduction of cyclin E/D1 and Cdk 2/4 expression level Anticancer activity *in vivo* in Balb/c mice • Inhibited the growth of tumor mass	[57]
Momordica charantia leaves and fruit 50 % methanolic extract	Anticancer activity in C57 Bl hybrid mice • ↑ life span • ↓ tumor volume • ↑ tumour growth inhibition rate	[58]
Alpha momorcharin	Cytotoxicity against B16 cells	[59]
Aqueous extract of *Allium sativum*	↓ viability of B16F10 cells Tumor inhibitory and normal cell (blood lymphocytes) protection property	
Ajoene	Inhibit tumor cell growth *in vitro* (B16/BL6) Inhibit B16/BL6 melanoma cell adhesion to LEC1 endothelial cells Lungs metastasis in C57BL/6 mice ↓ lungs metastasis Anticancer activity in C57 BL/6 mice ↓ tumor volume ↓ the expression of TNF-α and IL-6	[60]
Aqueous garlic extract and its fractions	Cytotoxic activities on Sk-mel3 cell line	[61]

Solanum nigrum aqueous extract	• ↓ cell viability • Inhibited B16-F1 cell migration and invasion • ↓ tumor weight and lung metastatic nodules • ↓ serum MMP-9 as well as Akt activity and PKCR, Ras, and NF-κB protein expressions	62
Solanum nigrum aqueous extract	• Cytotoxicity in A-375 cells • ↓ ROS level and the risk of melanoma development	63
Ocimum sanctum, Ocimum gratissimum, Ocimum basilicum, Ocimum canum, and Ocimum Kilimanscharicum hydroalcoholic extract	• Anticancer activity in C57 BL mice • ↓ tumor volume • ↑ life span	64
Ocimum sanctum leaves aqueous extract	Anticancer activity in C57 BL hybride mice • ↓ tumor volume • ↑ life span	65
Ocimum kilimandscharicum leaves essential oil	Selectivity and potent anticancer activity against UACC-62	66
Rhizophora apiculate methanolic extract	Anticancer activity against in in BALB/c mice • ↓ tumor volume • ↑ life span • ↓ tumor cell glutathione (GSH) levels and serum γ-glutamyl transpeptidase (GGT) and nitric oxide (NO) levels in the tumor-bearing animals • ↑ white blood cell count and hemoglobin • Anti-inflammatory activity	67
Rhizophora apiculate methanolic extract	Lungs metastasis in C57BL/6 mice • ↓ pulmonary tumor nodule formation • ↑ life span • ↓collagen hydroxyproline, hexosamine, uronic acid content, serum nitric oxide (NO), γ-glutamyl transpeptidase (GGT) and sialic acid level	68
Lithospermum erythrorhizon root hexane extract	• ↓ viability of B16F10 cells • Down regulation of anti-apoptotic Bcl-2 family proteins • Up regulation of apoptotic Bax protein expression • Induced cleavage of poly (ADP-ribose) polymerase (PARP) • Activate the caspase cascade (caspase 3) with this cleavage mediating the apoptosis of B16F10 cells • Sub-G1 cell cycle arrest Anticancer activity in C57BL/6 mice • ↓ tumor volume and weight • ↑ necrotic cells	69
Shikonin	• Inhibits angiogenesis • Inhibited proliferation and migration of endothelial cells • Blocking integrin alpha v beta 3 expression	70
Shikonin	• Induces apoptosis and prosurvival autophagy in A375 cells via ROS-mediated ER stress and p38 pathways	71

Shikonin	• Inhibits proliferation of melanoma cells (A375SM) by MAPK pathway-mediated induction of apoptosis • Increased nucleus and chromatin condensation and early/late apoptosis • Increased the pro-apoptotic proteins and decreased the anti-apoptotic proteins Anticancer activity against in in BALB/c nude mice • ↓ tumor volume and weight • ↑ apoptosis	[72]
Synadenium grantii latex	↓ B16F10 cell viability Cell cycle arrest in the S-G2/M phase Anticancer activity in C57BL/6 mice • ↓ tumor volume and weight • ↑ necrotic cells	[73]
Zingiber officinale supercritical carbon dioxide fluid extract	• Antioxidant activity Anticancer activity against *in vivo* xenograft model in BALB/c nu/nu female mice • ↓ tumor volume and tumor weight	[74]
[6]-Gingerol	• Inhibited both the VEGF- and bFGF-induced proliferation of human endothelial cells • Cell cycle arrest in the G1 phase • Blocked capillary-like tube formation by endothelial cells • Inhibited sprouting of endothelial cells in the rat aorta and formation of new blood vessel Lungs metastasis in C57BL/6 mice • Reduced the number of lung metastasis nodules	[75]
6-shogaol	Cytotoxicity against SK-MEL-2 cells	[76]
Decalepis hamiltonii root hydroalcolohic extract	Lungs metastasis in C57BL/6 mice • ↓ number of lung metastasis nodules • ↓ lung collagen hydroxyproline, hexosamine, and uronic acid levels • ↓ serum sialic acid and γ-glutamyl transpeptidase • ↓ proinflammatory cytokines (IL-1β, IL-6, TNF-α, IL-2, and GM-CSF) in B16F10 cells • ↓ serum NO level • Inhibit the activation and nuclear translocation of • p65 and p50 subunits of nuclear factor κB in B16F-10 cells	[77]
Limoniastrum guyonianum aqueous extract	• Inhibited B16F10 cell proliferation • Apoptotic changes in the B16F10 cells (nuclear condensation) • Induces apoptosis on B16F10 cells Anticancer activity against in in BALB/c mice • ↓ tumor volume • ↑ splenocytes proliferation • ↑ NK and CTL activities in tumor-bearing mice • promoted lysosomal activity of host macrophages	[78]
Rhodiola crenulate root extracts	• ↑ cell death and reduction in tumor cell proliferation • ↓ cellular migration • ↓ expression of integrin β1 and vimentin • ↓ in mitotic activity, and ↑ in tumor necrosis	[79]

Panax ginseng	Anticancer activity in C57/BL mice • ↓ tumor volume • ↓ tumor weight • Stimulate the proliferation of T lymphocyte	[80]
Methanolic extract of *Panax ginseng* root	Anticancer activity in C57BL/6 mice • ↓ tumor volume • potentiate NK cell activity • ↑ IFNγ content • Enhance the expression of cytotoxic mediators & IL-2 responsiveness in the early effector phase and the constitutive expression of granzyme B	[81]
Ginsenoside Rk1	• Cytotoxicity against SK-MEL-2 human melanoma • Induces DNA fragmentation and morphological changes • Induction of apoptosis in SK-MEL-2 through both extrinsic and intrinsic pathways • Up-regulation of Fas, FasL, and Bax protein expression • Down-regulation of procaspase-8, procaspase-3, mutant p53 and Bcl-2 protein expression	[82]
Ginsengmarc-derived low-molecularweight oligosaccharide	• Enhance the production of TNF-α, IL-6, and NO • Induce the phosphorylation of c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), p38, and nuclear factor κB (NFκB) • Anticancer activity *in vitro* against melanoma cells by potentiating macrophage function	[83]
Ginsenoside F1	• ↓ proliferation of B16 cells • Induced morphological change and clustering of B16 melanoma cells • Block the melanin production of B16 cells	[84]
ginsenoside Rg3	• Inhibit proliferation of B16 cells • Regulate cell cycle • Alter cellular morphology (flat cell morphology, loss of nucleoli, reduction of mitotic figures, and weaker alkalophilic quality of cytoplasm, reduced volume, condensed chromatin, nuclear fragmentation, and apoptotic bodies) • Cell cycle arrest (G1 block, G2 block, G2-M cells) • Induce cell apoptosis *in vitro* (↓noncleaved caspase-3 and Bcl-2) • Blocking angiogenesis Lungs metastasis in C57BL/6 mice • ↓ inhibition of the tumor metastasis • ↓ lung weight • ↓ density of microvessels • ↓ metastasis nodules • ↑ survival time	[85]
Ginsenoside Rh2	Anticancer activity in C57/BL mice • ↓ tumor volume • ↑ life span • Enhanced $CD4^+$ and $CD8a^+$ T-lymphocyte infiltration in the tumor	[86]

	• Triggered cytotoxicity in spleen lymphocytes	
Panaxydol	Decreased markedly the proliferation of SK-MEL-1 Inhibited cell cycle progression at G1-S transition ↑ $p27^{KIP1}$ expression ↓ Cdk2 activity	[87]
Lipid-Soluble Ginseng Extract	Inhibited invasion and migration of B16F10 cells Lungs metastasis in C57BL/6 mice • ↓ inhibition of the tumor metastasis • ↓ mRNA and protein levels of MMP-2 in B16F10 cells	[88]
Ginsenoside 20-O-b-D-Glucopyranosyl-20(S)-Protopanaxadiol	Induces autophagy and apoptosis in human melanoma via AMPK/JNK phosphorylation	[89]
Resveratrol	Induce G1/S cell cycle arrest of A375 and SK-MEL-31 Induced the apoptosis in A375 and SK-MEL-31 cells by upregulating the expression of Bcl-2-associated X protein and B-cell lymphoma 2	[90]
Resveratrol	Upregulation of quinone reductase 2 and p53 in human melanoma Line IV clone 1 and clone 3 cells	[91]
Resveratrol	Downregulation of surviving transcription through the suppression of of β-catenin STAT3	[92]
Resveratrol	• Inhibit proliferation of B16F10 cells via the regulation of levels of AMPK, COX-2, VASP and VEGF • Reduced the number of microvascular vessels • Inhibit cellular migration Anticancer activity in Balb/c nu/nu mice • ↓ tumor volume	[93]
Resveratrol	Induce autophagy through the ceramide accumulation and inhibition of Akt/mTOR pathway in B16 Cells	[94]
Resveratrol	• ↓ angiogenesis (blocks both VEGF- and FGF-receptor mediated angiogenic responses) • Inhibits the phosphorylation of mitogen-activated protein kinase isoforms ($MAPK^{p44}$/$MAPK^{p42}$) • ↓ tumor growth • ↓ wound healing	[95]

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