MINI-REVIEW

Anticancer Activity of Essential Oils: Targeting of Protein Networks in Cancer Cells

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Abstract

Cancer is a multifaceted and genomically complex disease and research over decades has gradually and sequentially shown that essential biological mechanisms including cell cycle arrest and apoptosis are deregulated. The benefits of essential oils from different plants have started to gain appreciation as evidenced by data obtained from cancer cell lines and xenografted mice. Encouraging results obtained from preclinical studies have attracted considerable attention and various phytochemicals have entered into clinical trials.

Keywords: Essential oils - cancer - apoptosis - signaling

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Introduction

Data obtained through high throughput technologies is improving our understanding about convergent and divergent pathways that operate in different cancers. Genetic, genomic and proteomic studies have added new layers of knowledge and it is now known that genetic/epigenetic mutations, overexpression of oncogenes, inactivation of tumor suppressor genes contribute to malignant transformation of cancer progenitor cells. Increasingly it is being realized that there is a dysregulation of spatio-temporally controlled cellular signaling cascades that modulate normal growth and tissue homeostasis. Apoptosis is a programmed cell death and it is now well established that cancer cells escape from cell death. Confluence of information also indicated some other factors which play a role in cancer including genomic instability and oncogenic fusion proteins. BCR-ABL is a fusion oncoprotein that makes leukemic cells difficult to target (Farooqi et al., 2013). TMPRSS2-ERG is another fusion transcript identified in prostate cancer cells and recently emerging *in-vitro* and *in-vivo* studies are focusing on targeting of the protein product of TMPRSS2-ERG (Farooqi et al., 2014). In addition to overwhelmingly increasing list of potential oncogenic and tumor suppressor proteins which underlie tumour development and progression, tumor microenvironment also plays a significant role and communicates with cancer cells.

We would give an overview of newly emerging experimental evidence addressing different molecular mechanisms reported to be regulated by these phytochemicals.

In-vitro Analysis of Different Essential Oils

Essential oil (EO) of *Artemisia vulgaris* has been reported to induce apoptosis in HL-60 leukemic cell line by promoting release of cytochrome c. Moreover, Caspase were also functionally active upon treatment with essential oils (Saleh et al., 2014). Citral is a bioactive ingredient present in Essential oil obtained from *Melissa officinalis*. It has recently been shown to induce apoptosis in Glioblastoma Multiforme cells via enhancing ROS generation and activating caspase-3 (Queiroz et al., 2014). There was notably enhanced expression of caspase-3 and Bax in gastric cancer cell line SGC-7901 upon treatment with Essential oils from Toona *sinensis*. Detailed chemical analysis of Essential oil indicated that there was a higher percentage of sesquiterpenes including β-caryophyllene, β-eudesmene, copaene and caryophyllene as evidenced by GC/MS (Wu et al., 2014). Essential oil from *Lavandula angustifolia* was effective against MCF-7 and HeLa cell lines. It exerted its biological effects via enhancing Bax expression (Tayarani-Najaran et al., 2014). Essential oil from *Curcuma zedoaria roscoe* was noted to effectively induced apoptosis in non-small cell lung carcinoma H1299 cells. Results obtained from *in-vitro* analysis

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Table 1. Bioactive Ingredients of Essential Oils

Bioactive Ingredients	Source	Cancer Cell Lines	Reference
Precocene	*Ageratum conyzoides* and *Lippia multiflora*	LNCaP and PC-3	Bayala et al., 2014
α-terpineol and β-caryophyllene/ β-caryophyllene, thymol, γ-terpinene and thymyle acetate	*Ocimum basilicum* and *Lippia multiflora*	SF-767 glioblastoma	Bayala et al., 2014
Thymoquinone	*Nigella sativa*	HeLa	Sakalar et al., 2013
Terpinen-4-ol, monoterpene		HL-60	Banjerdpongchai and Khaw-On, 2013
Anthocyanin	Methanolic extracts	HepG2	Banjerdpongchai et al., 2013

suggested that phosphorylated levels of JNK1/2 and p38 were considerably enhanced. However, there was a slight reduction in pERK1/2 levels and pro-survival pathways including AKT/NF-ϰB were significantly inhibited in H1299 cells. Downregulation was noted for Bcl-2 and Bcl-xL in H1299 cells. It is also relevant to mention that intra-peritoneally administered zedoary essential oil remarkably inhibited tumor growth in mice xenografted with H1299 cells (Chen et al., 2014). Patchouli alcohol is a bioactive components isolated from essential oil of *Pogostemon cablin* exerted its inhibitory effects on expression levels of cyclin D1 and cyclin-dependent kinase 4 (CDK4) in colorectal cancer cells. Expression and biological activity of HDAC2 (histone deacetylase 2) were also remarkably repressed. NFKB was active in treated cancer cells as evidenced by an increase in nuclear translocation of p65 (Jeong et al., 2013). Cyclin D1 and CDK4 were also substantially reduced in pancreatic cancer cells after treatment with Frankincense essential oil. Akt and Erk1/2 were noted to be activated in treated cancer cells (Ni et al., 2014). Certain hints have emerged emphasizing on the fact that allyl isothiocyanate impressively induced apoptosis in wild type p53 containing bladder cancer cells. Contrarily it did not induce apoptosis in mutant p53 containing bladder cancer cells (Savio et al., 2014). There is an exciting piece of evidence suggesting that partially hydrogenated α-zingiberene isolated from essential oil from Casearia sylvestris was effective against B16F10-Nex2 cell line. However, surprisingly, fully hydrogenated derivative was effective against MCF-7 and B16F10-Nex2 (Bou et al., 2013).

Essential oil from Monarda citriodora has been noted to functionalize extrinsic and intrinsic pathways of apoptosis. There was an upregulated expression of death receptors including Fas and TNF-R1 in treated cancer cells. Methodologies also revealed notably enhanced mitochondrial membrane permeability and increase expression of caspase-9. Intriguingly, PI3K/AKT/mTOR pathway was also inhibited significantly in treated HL-60 cells (Pathania et al., 2013). It is interesting to note that bioactive components in essential oil extracted from *Dracocephalum multicaule* protected K562 cells from oxidative stress (Esmaeili et al., 2014). Essential oil obtained from *Smyrnium olusatrum* also induced apoptosis in colon carcinoma cells (Quassinti et al., 2014).

Xenografted mice

It has previously been persuasively revealed that essential oils of *Tridax procumbens* and *Tridax procumbens* considerably inhibited lung metastasis in mice xenografted with B16F-10 melanoma cells (Manjamalai et al., 2012; Manjamalai and Grace, 2013). Frankincense essential oil induced tumor regression in mice subcutaneously implanted with MIA PaCa-2 cells (Ni et al., 2014). Essential oil of *Lippia gracilis* considerably inhibited tumor growth in xenografted mice (Ferraz et al., 2013). Flavonoids isolated from *Oxytropis falcata* significantly inhibited tumor growth in mice transplanted with H22 cells (Yang et al., 2013). Essential oils from *Wedelia chinensis* have also shown notable anticancer activity in mice xenografted with B16F-10 cells (Manjamalai and Berlin Grace, 2012).

In vitro analysis of Efficacy of Elemene

It has been shown that Elemene effectively improved cisplatin sensitivity in MCAS and A2780/CP70 human ovarian carcinoma cells by exerting its inhibitory effects on expression of an anti-apoptotic gene, XIAP. Moreover, cisplatin induced ERCC-1 was also significantly inhibited in Elemene treated carcinoma cells (Li et al., 2013). Elemene has been shown to stimulate the expression of Caspase-3 and Cytochrome C in lung cancer A549 cells, thus overcoming drug resistance and improving cisplatin mediated apoptosis in A549 cancer cells (Yao et al., 2014). Chemically improved β-elemene derivative has been designed with a cis-2, 6-dimethylpiperazine substitution and noted to be efficient in substantially reducing phosphorylated levels of 4EBP1 and p70S6K1 in MCF-7 and MDA-MB-468 cells (Ding et al., 2013). It has recently been convincingly revealed that gene silencing of mTOR in lung adenocarcinoma A549 cells notably enhanced Elemene induced apoptosis (Zou et al., 2014). There is exciting piece of evidence suggesting that ERK1/2-Bcl-2/survivin pathway was remarkably inhibited in Elemene treated U87 glioblastoma cells. Elemene mediated inhibitory effects were enhanced upon treating cells with ERK1/2 inhibitors. Furthermore, efficacy of temozolomide was also improved in Elemene treated glioblastoma cells (Zhu et al., 2014).

In vitro and *in vivo* analysis of Efficacy of Perillyl Alcohol (POH)

Conjugate of temozolomide to POH (NEO212) has recently been tested for its efficacy in immune incompetent mice xenografted with Temozolomide-Resistant Gliomas. Results revealed that there was considerably reduced intracranial tumor growth in xenografted mice treated with NEO212 (Cho et al., 2014). NEO212 has also produced encouraging results in an intracranial mouse tumor model with triple-negative breast cancer as median survival of cancer model was increased. NEO212 mediated DNA damage was more notable as compared to temozolomide (Chen et al., 2014). POH has also been noted to suppress protein levels of telomerase catalytic subunit reverse

transcriptase (hTERT). Mechanistically it was shown that different proteins including hTERT-mTOR-RAPTOR assembled to form multi-protein complex which was dissociated in POH treated prostate cancer cells (Sundin et al., 2013).

In vitro analysis of Efficacy of Limonene

Limonene has been shown to activate ERK pathway in lymphoma cell line to induce apoptosis (Manuele et al., 2010). Limonene effectively induced apoptosis in LS174T colon cancer cells by inhibiting phosphorylation of Akt and GSK-3β. Moreover, intrinsic pathway was noted to be activated in Limonene treated LS174T colon cancer cells (Jia et al., 2013). Limonene and docetaxel synergistically induced greater ROS production and considerably enhanced apoptosis in prostate cancer cells (Rabi and Bishayee, 2009).

References

Bayala B, Bassole IH, Gnoula C, et al (2014). Chemical composition, antioxidant, anti-inflammatory and anti-proliferative activities of essential oils of plants from burkina faso. *PLoS One*, **9**, 92122.

Bou DD, Lago JH, Figueiredo CR, et al (2013). Chemical composition and cytotoxicity evaluation of essential oil from leaves of Casearia sylvestris, its main compound α-zingiberene and derivatives. *Molecules*, **18**, 9477-87.

Chen CC, Chen Y, Hsi YT, et al (2013). Chemical constituents and anticancer activity of *Curcuma zedoaria roscoe* essential oil against non-small cell lung carcinoma cells *in vitro* and *in vivo*. *J Agric Food Chem*, **61**, 11418-27.

Chen TC, Cho HY, Wang W, et al (2014). A novel temozolomide-perillyl alcohol conjugate exhibits superior activity against breast cancer cells *in vitro* and intracranial triple-negative tumor growth *in vivo*. *Mol Cancer Ther*. **13**, 1181-93.

Cho HY, Wang W, Jhaveri N, et al (2014). NEO212, Temozolomide Conjugated to Perillyl Alcohol, is a Novel Drug for Effective Treatment of a Broad Range of Temozolomide-Resistant Gliomas. *Mol Cancer Ther*, **13**, 2004-17.

Ding XF, Shen M, Xu LY, et al (2013). 13, 14-bis (cis-3,5-dimethyl-1-piperazinyl)-β-elemene, a novel β-elemene derivative, shows potent antitumor activities via inhibition of mTOR in human breast cancer cells. *Oncol Lett*, **5**, 1554-8.

Esmaeili MA, Sonboli A, Mirjalili MH (2014). Oxidative stress protective effect of *Dracocephalum multicaule* essential oil against human cancer cell line. *Nat Prod Res*, **28**, 848-52.

Ferraz RP, Bomfim DS, Carvalho NC, et al (2013). Cytotoxic effect of leaf essential oil of *Lippia gracilis* Schauer (Verbenaceae). *Phytomedicine*, **20**, 615-21.

Jeong JB, Choi J, Lou Z, et al (2013). Patchouli alcohol, an essential oil of *Pogostemon cablin*, exhibits anti-tumorigenic activity in human colorectal cancer cells. *Int Immunopharmacol*, **16**, 184-90.

Jia SS, Xi GP, Zhang M, et al (2013). Induction of apoptosis by D-limonene is mediated by inactivation of Akt in LS174T human colon cancer cells. *Oncol Rep*, **29**, 349-54.

Li QQ, Lee RX, Liang H, et al (2013). β-Elemene enhances susceptibility to cisplatin in resistant ovarian carcinoma cells via downregulation of ERCC-1 and XIAP and inactivation of JNK. *Int J Oncol*, **43**, 721-8.

Manjamalai A, Berlin Grace VM (2012). Antioxidant activity of essential oils from *Wedelia chinensis* (Osbeck) *in vitro* and *in vivo* lung cancer bearing C57BL/6 mice. *Asian Pac J Cancer Prev*, **13**, 3065-71.

Manjamalai A, Grace VM (2013). The chemotherapeutic effect of essential oil of *Tridax procumbens* (Lour) on lung metastasis developed by B16F-10 cell line in C57BL/6 mice. *Cancer Invest*, **31**, 74-82.

Manjamalai A, Kumar MJ, Grace VM (2012). Essential oil of *Tridax procumbens* L induces apoptosis and suppresses angiogenesis and lung metastasis of the B16F-10 cell line in C57BL/6 mice. *Asian Pac J Cancer Prev*, **13**, 5887-95.

Manuele MG, Barreiro Arcos ML, Davicino R, et al (2010). Limonene exerts antiproliferative effects and increases nitric oxide levels on a lymphoma cell line by dual mechanism of the ERK pathway: relationship with oxidative stress. *Cancer Invest*, **28**, 135-45.

Ni X, Suhail MM, Yang Q, et al (2012). Frankincense essential oil prepared from hydrodistillation of Boswellia sacra gum resins induces human pancreatic cancer cell death in cultures and in a xenograft murine model. *BMC Complement Altern Med*, **12**, 253.

Pathania AS, Guru SK, Verma MK, et al (2013). Disruption of the PI3K/AKT/mTOR signaling cascade and induction of apoptosis in HL-60 cells by an essential oil from Monarda citriodora. *Food Chem Toxicol*, **62**, 246-54.

Quassinti L, Maggi F, Barboni L, et al (2014). Wild celery (Smyrnium olusatrum L.) oil and isofuranodiene induce apoptosis in human colon carcinoma cells. *Fitoterapia*, **97**, 133-41.

Queiroz RM, Takiya CM, Guimarães LP, et al (2014). Apoptosis-inducing effects of *melissa officinalis* L. essential oil in glioblastoma multiforme cells. *Cancer Invest*, **32**, 226-35.

Rabi T, Bishayee A (2009). d-Limonene sensitizes docetaxel-induced cytotoxicity in human prostate cancer cells: Generation of reactive oxygen species and induction of apoptosis. *J Carcinog*, **8**, 9.

Sakalar C, Yuruk M, Kaya T, et al (2013). Pronounced transcriptional regulation of apoptotic and TNF-NF-kappa-B signaling genes during the course of thymoquinone mediated apoptosis in HeLa cells. *Mol Cell Biochem*, **383**, 243-51.

Saleh AM, Aljada A, Rizvi SA, et al (2014). In vitro cytotoxicity of Artemisia vulgaris L. essential oil is mediated by a mitochondria-dependent apoptosis in HL-60 leukemic cell line. *BMC Complement Altern Med*, **14**, 226.

Savio AL, da Silva GN, de Camargo EA, et al (2014). Cell cycle kinetics, apoptosis rates, DNA damage and TP53 gene expression in bladder cancer cells treated with allyl isothiocyanate (mustard essential oil). *Mutat Res Fundam Mol Mech Mutagen*, **762**, 40-6.

Sundin T, Peffley DM, Hentosh P (2013). Disruption of an hTERT-mTOR-RAPTOR protein complex by a phytochemical perillyl alcohol and rapamycin. *Mol Cell Biochem*, **375**, 97-104.

Tayarani-Najaran Z, Amiri A, Karimi G, et al (2014). Comparative studies of cytotoxic and apoptotic properties of different extracts and the essential oil of Lavandula angustifolia on malignant and normal cells. *Nutr Cancer*, **66**, 424-34.

Wu JG, Peng W, Yi J, et al (2014). Chemical composition, antimicrobial activity against Staphylococcus aureus and a pro-apoptotic effect in SGC-7901 of the essential oil from *Toona sinensis* (A. Juss.) Roem. leaves. *J Ethnopharmacol*, **154**, 198-205.

Yang GM, Yan R, Wang ZX, et al (2013). Antitumor effects of two extracts from Oxytropis falcata on hepatocellular carcinoma *in vitro* and *in vivo*. *Chin J Nat Med*, **11**, 519-24.

Yao CC, Tu YR, Jiang J, et al (2014). β-elemene reverses the drug resistance of lung cancer A549/DDP cells via the

mitochondrial apoptosis pathway. *Oncol Rep*, **31**, 2131-8.
Zhu TZ, Li XM, Luo LH, et al (2014). β-Elemene inhibits proliferation through crosstalk between glia maturation factor β and extracellular signal-regulated kinase 1/2 and impairs drug resistance to temozolomide in glioblastoma cells. *Mol Med Rep*, **10**, 1122-8.
Zou K, Tong E, Xu Y, et al (2014). Down regulation of mammalian target of rapamycin decreases HIF-1α and survivin expression in anoxic lung adenocarcinoma A549 cell to elemene and/or irradiation. *Tumour Biol*, 2014 Jun 28.