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Anticancer Activity of *Boswellia* (Frankincense) Essential Oil

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ABSTRACT

Epidemiological studies have showed that regular consumption of phytochemicals is strongly associated with a reduced risk of cancer. The gum resin of the Boswellia species has been used traditionally in Ayurvedic medicine to treat inflammatory conditions. Recent experimental data from cell culture, preclinical and clinical studies strongly suggests the potential use of Boswellia essential oil (frankincense) for the prevention and/or treatment of wide variety of cancers including pancreatic, breast, prostate, blood, colorectal, brain, skin, bladder and hepatic cancers. Analysis of the ingredients of these extracts revealed that the pentacyclic triterpenes boswellic acids (BAs) possess biological activities and appear to be responsible for the respective anticancer activity. One such agent is acetyl-11-keto-beta-boswellic acid (AKBA), which shows promise for potential use as an effective anticancer agent.

***Key words*:** *Boswellia*, Frankincense, Boswellic acids, Cancer

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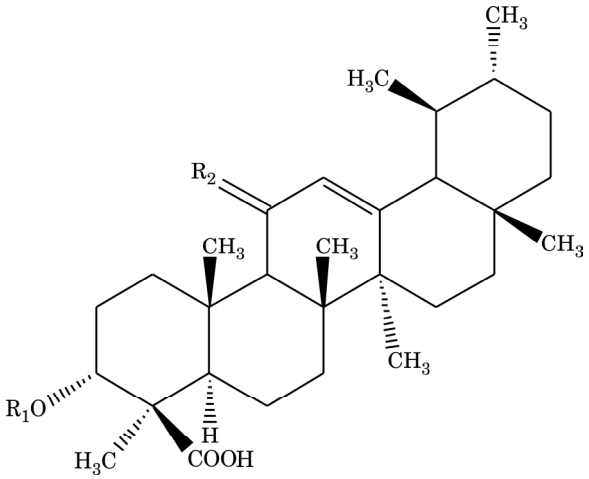
INTRODUCTION

Traditional medicines have been used for thousands of years and many are still used today by a large percentage of the world's population. Natural products are generally considered to be safe, inexpensive and specifically target many diseases. Aromatic gum resin obtained from trees of the genus *Boswellia* (family *Burseraceae*), also known as frankincense or olibanum, has been used for many centuries as folk medicine in Asia and Africa for the treatment of diverse diseases. *Boswellia* are deciduous trees that have numerous species and varieties including *Boswellia serrata* in India, *Boswellia carteri* in East Africa and China, and *Boswellia sacra* in Arabia, each producing a slightly different type of resin (Maloney, 1997; Nishimura *et al*., 2006; Langmead and Rampton, 2006). Incisions are made in the trunks of the trees to produce exuded gum that has the appearance of a milk-like resin. Upon exposure to air, the resin hardens into orange-brown gum known as frankincense. Frankincense oil, an extract prepared by steam distillation from frankincense gum, is one of the most commonly used oils in aromatherapy and is also used in incense, as a fixative in perfumes, fumigants, and religious rituals (Maloney, 1997). In addition, the gum resin of *Boswellia* is used in Ayurvedic medicine, a traditional form of herbal medicine native to India, for the treatment of inflammatory diseases such as rheumatoid arthritis, Crohn's disease and other inflammatory, respiratory, and liver disorders (Nishimura *et al*., 2006; Langmead and Rampton, 2006). In addition, *Boswellia* extracts were used as antibacterial, antifungal, immunomodulatory and antihyperlipidemic agents (Mikhaeil *et al*., 2003; Weckesser *et al*., 2007). Recent investigations have shown that boswellic acids from *Boswellia* extracts possess potent anticancer activities through their antiproliferative and apoptotic effects in multiple human cancer cell lines and in mice (Huang *et al*., 2000; Eichhorn *et al*., 2011; Ni *et al*., 2012). The present review will discuss in detail the beneficial effects of *Boswellia* resin essential oils as an anticancer agent.

Chemical Composition of *Boswellia* Essential Oil

Modern analytical techniques allowed isolating several compounds from *Boswellia* species including boswellic acids, lupeolic acid, elemonic acid, ursolic acid, incensole, tirucallic acid, cembrene, amyrin, and verticillatriene (Akihisa *et al*., 2006; Poeckel and Werz, 2006; Fu-Shuang *et al*., 2010). Extensive research during the last thirty years has identified the most active components of the resin as boswellic acids,

which are pentacyclic triterpenes, and their derivatives (Takada *et al*., 2006). Pentacyclic triterpenes (PTs) are widely distributed among plants, but due to the complex biosynthesis steps including cyclization of squalene, only higher plants are capable to synthesize these compounds (Poeckel and Werz, 2006). The most important source for bioactive PTs are constitutes of the *Boswellia* species. Previous studies have indicated that the β-configuration boswellic acids showed superior activity over the respective α-isomers (Poeckel and Werz, 2006). The most commonly studied acids from *Boswellia* species gum resins are β-boswellic acid, 11-keto-β-boswellic acid (KBA), 3-*O*-acetyl-β-boswellic acid and 3-*O*-acetyl-11-keto-β-boswellic acid (AKBA) (Fig. 1), and these compounds are the most active constituents reported for their anti-inflammatory, anti-proliferative and cytotoxic activities (Huang *et al*., 2000; Poeckel and Werz, 2006). In addition to boswellic acids, tetracyclic triterpenes such as 3-α-acetoxy-tirucallic acid and 3-β-acetoxy-tirucallic acid, also isolated from *Boswellia* species, showed potent anticancer activity against prostate cancer cells (Estrada *et al*., 2010).



R_1	R_2	Derivative
H	H_2	β-Boswellic acid (**BA**)
Ac	H_2	3-*O*-Acetyl- β-Boswellic acid (**ABA**)
H	O	11-Keto- β-Boswellic acid (**KBA**)
Ac	O	3-*O*-Acetyl-11-Keto- β-Boswellic acid (**AKBA**)

Fig. 1: Chemical structures of β-boswellic acid and its derivatives.

Boswellia Essential Oil (Frankincense) as an Anticancer Agent

Cancer is a hyperproliferative disorder that can metastasis into the vital organs of the body through invasion and angiogenesis. Compounds from *Boswellia* essential oil block the transformation, proliferation, and invasion of tumor cells. A large body of evidence has accumulated over the past three decades demonstrating that frankincense oil targets several steps in cancer biochemical pathways. Bioactive compounds from *Boswellia* essential oil have been shown to suppress transformation, proliferation, and metastasis of tumors. These effects are mediated through its regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes. They also inhibit proliferation of cancer cells by inducing cell cycle arrest in various phases of the cell cycle and by inducing apoptosis. In addition, boswellic acids including AKBA have been shown to possess protective and therapeutic effects through their cytostatic and apoptotic effects against multiple cancers including brain, blood, liver, pancreas, breast, prostate, colon and skin cancer cells. Recent studies are identified the molecular mechanisms involved in mediating the anticancer effects of *Boswellia* essential oil. In one such study, boswellic acids were tested against a National Cancer Institute (NCI, National Institutes of Health, USA) panel of human tumor cell lines consists of leukemia, melanoma, non-small cell lung cancer, colon cancer, renal cancer, ovarian cancer, tumor cells of the central nervous system, prostate carcinoma, and breast cancer was employed to determine the cytotoxicity of boswellic acids (Eichhorn *et al*., 2011). The cytotoxicity of boswellic acids towards the NCI cell line panel was evaluated by determining the IC_{50} (concentration resulting in 50% inhibition) and was found to display a potency that ranged between 10^{-8} to 10^{-4} M. Prostate cancer cells were most sensitive to boswellic acids, while breast cancer and leukemia cell lines were the most resistant (Eichhorn *et al*., 2011).

Pancreatic Cancer

In a recent study, treatment of human pancreatic cancer cells PANC-28 with AKBA suppressed cysteine X cysteine chemokine ligand 12 (CXCL12)-induced invasion of these cells (Park *et al*., 2011a). CXCL12 is one of the best studied chemokines in tumor cell migration and metastasis. Chemokine receptor 4 (CXCR4) binds to its ligand CXCL12, leading to tumor migration, and agents that can interrupt the CXCR4–CXCL12 cell-signaling pathway have the potential to suppress tumor metastasis in wide variety of cancers. Results of this study showed that treatment of PANC-28 cells with AKBA for 12 hour reduced NF-êB

activation in a dose-dependent manner. These results suggest that AKBA may downregulate CXCR4 expression by suppressing NFêB activation. In another experiment, PANC-28 cells were implanted in the pancreas tails of nude mice (Park *et al*., 2011a). After a week, treatment was started and continued for 4 weeks, and animals were sacrificed 6 weeks after tumor cell injection. The result of immunohistochemical and Western blot analyses showed that AKBA suppressed the expression of CXCR4 in human pancreatic tumor tissues. In addition, AKBA significantly reduced tumor growth and metastasis to spleen, liver and lung (Park *et al*., 2011a). Furthermore, AKBA suppressed the proliferation of four pancreatic cancer cell lines (AsPC-1, BxPC-3, MIA PaCa-2, and PANC-28) and downregulated the expression of antiapoptotic (Bcl-2, Bcl-xL, and survivin), proliferative (COX-2, c-myc, and cyclin D1), and metastatic (MMP-9, CXCR4) proteins in a dose-dependent manner (Park *et al*., 2011b). Moreover, AKBA potentiated the apoptotic activity of gemcitabine in pancreatic cancer cells by enhancing caspase-mediated cleavage of PARP induced by gemcitabine. AKBA suppressed distant organ metastasis in mice previously implanted with PaCa-2 cells, and these cells were found in the spleen, liver and lungs of vehicle-treated mice. AKBA alone suppressed metastasis to those organs; however, the combination of AKBA and gemcitabine inhibited metastasis significantly more in these mice and completely suppressed metastasis to the lung. AKBA inhibited Ki-67 (marker for cell Proliferation) and CD31 (a marker for microvessel density) expression in tumor tissues, and this effect was enhanced in case of combined AKBA and gemcitabine treatment. Similarly, AKBA alone suppressed the constitutive activation of NF-κB in the pancreatic tumor tissue, and this downregulation was enhanced in tissue obtained from animals treated with both AKBA and gemcitabine together. AKBA significantly downregulated the expression of proteins related to antiapoptosis (Bcl-xL), proliferation (cyclin D1, c-myc), metastasis (CXCR4) and invasion (MMP-9, ICAM-1). Besides, HPLC analysis results have showed that serum levels of AKBA could be detected in plasma and pancreatic tissue 4 hr after oral administration of drug in mice, and there is a strong correlation between tumor regression and the amount of AKBA in the blood (Park *et al*., 2011b).

Studies by Ni reported that frankincense essential oil from *Boswellia sacra* gum resins is highly effective in suppressing proliferation and inducing apoptosis of human pancreatic cancer cell lines (Ni *et al*., 2012). Results showed that *Boswellia* essential oil significantly induced cytotoxicity of human pancreatic cancer cell lines MIA PaCa-2 and Panc-28 after acute treatment in a concentration dependent manner, while

DANG and BxPC-3 cells were more resistant to essential oil-induced death. Results of TUNEL assay, a quantitative method to determine cells undergoing apoptosis, showed significantly higher numbers of TUNEL-positive cells detected in the group receiving frankincense essential oil than the control. In addition, essential oil activated the caspase-dependent apoptotic pathway, induced a rapid and transient activation of Akt and Erk1/2, and suppressed levels of cyclin D1 and cdk4 expression in cultured pancreatic cancer cells. Moreover, in a xenograft mouse model, mice bearing human pancreatic cancer MIA PaCa-2 cells were weighted before and after frankincense essential oil treatment and tumor volumes were determined *in situ*. Results showed that significantly smaller tumors were observed in frankincense essential oil-treated animals as compared to the control group (Ni *et al*., 2012).

Breast Cancer

The essential oil from *Boswellia sacra* was investigated for its antitumor properties against a panel of human breast cancer cell lines T47D, MCF-7, and MDA-MB-231 cells, as well as immortalized normal breast epithelial MCF-10-2A (Suhail *et al*., 2011). Results showed that this essential oil suppressed cell viability in all three human breast cancer cell lines, whereas immortalized normal breast epithelial MCF10-2A cells were resistant to the same treatment. In addition, *Boswellia sacra* essential oil induced genomic DNA fragmentation in a time-dependent manner; and all three human breast cancer cell lines exhibited similar patterns and visible fragmented genomic DNA within 8 hours post-treatment. In contrast, the same concentrations of essential oil treatment did not induce DNA fragmentation in MCF10-2A cells. Essential oil induced activated (cleaved) caspase-3 and cleaved PARP expression within 1 hour post-exposure to essential oils in breast cancer cells. *Boswellia sacra* essential oil was also found to completely blocked MDAMB-231 cell tube formation on Matrigel based on XTT assay. In addition, *Boswellia sacra* essential oil suppressed phospho-Akt and phospho- ERK1/2 expression in breast cancer cell lines, whereas MCF10-2A cells did not have detectable phosporylated ERK1/2 expression, and their phosphorylated Akt expression was not altered by essential oil treatment. *Boswellia sacra* essential oil also suppressed the expression of cell cycle regulators, cyclin D1 and cdk4. All three breast cancer cell lines responded to essential oils with suppressed cyclin D1 and cdk4 expression. In contrast, MCF10-2A cells did not respond to essential oil treatment with altered cdk4 expression, and had no detectable cyclin

D1expression. These results demonstrate that *Boswellia sacra* essential oil prepared from hydrodistillation has antiproliferative, pro-apoptotic, and anti-invasive activities in cultured breast cancer cells which may suggest some benefit for managing breast cancer in women, while having little or no effect on normal mammary epithelial cell viability (Suhail *et al.,* 2011). Park and coworkers (Park *et al*., 2011a), showed that treatment of breast cancer MDA-MB-231 cells with AKBA suppressed the CXCL12-induced invasion of these cells and down-regulated CXC4. It has also been found that the AKBA-mediated down-regulation of CXCR4 occurred at both the mRNA and protein levels (Park *et al*., 2011a).

Prostate Cancer

Syrovets and coworkers have shown that AKBA treatment could induce apoptosis in cultured androgen-independent PC-3 prostate cancer cells as shown by mitochondrial cytochrome c release and DNA fragmentation (Syrovets *et al*., 2005). At the molecular level, AKBA inhibited constitutively activated NFêB signaling as shown by impaired phosphorylation of p65 and reduced nuclear translocation of NFκB which was associated with downregulation of NFκB-dependent antiapoptotic proteins Bcl-2 and Bcl-x(L). In addition, AKBA reduced expression of cyclin D1 which is a crucial cell cycle regulator. Moreover, topical application of water-soluble AKBA-gamma-cyclodextrin on PC-3 tumors implanted onto chick chorioallantoic membranes induced concentration-dependent inhibition of proliferation and apoptosis (Syrovets *et al*., 2005). Furthermore, in nude mice implanted with PC-3 tumors, systemic application of AKBA-gamma-cyclodextrin inhibited tumor growth and triggered apoptosis in the absence of detectable systemic toxicity (Syrovets *et al*., 2005).

Yuan *et al*. showed that AKBA caused G1 cell cycle arrest which was accompanied by suppression of cyclin D1 and upregulation of p21 in prostate cancer cells (Yuan *et al.,* 2008). In addition, the growth inhibition of prostate cancer cells by AKBA was associated with a decrease of androgen receptor (AR) expression at mRNA and protein levels suggesting a useful role of AKBA as a therapeutic agent for prostate cancer in men (Yuan *et al.,* 2008).

Studies conducted by Lu *et al*. reported that AKBA has been found to induce apoptosis in LNCaP and PC-3 human prostate cancer cells (Lu *et al*., 2008). AKBA-induced apoptosis was correlated with the activation of caspase-3 and caspase-8 as well as with PARP cleavage.

The activation of caspase-8 was correlated with increased levels of death receptor (DR) 5, and AKBA-induced apoptosis, caspase-8 activation, and PARP cleavage were inhibited by knocking down DR5 using a small hairpin RNA. These results indicated that AKBA induces apoptosis in prostate cancer cells through a DR5-mediated pathway (Lu *et al*., 2008).

Other studies showed that daily treatment with 10 mg/kg AKBA suppressed tumor growth in xenograft mice bearing human prostate tumors (Pang *et al*., 2009). These studies also showed that AKBA treatment significantly inhibited blood vessel formation in mice and effectively suppressed vascular endothelial growth factor (VEGF)-induced microvessel formation in rat aortic ring assay. In addition, AKBA inhibited VEGF-induced cell proliferation, chemotactic motility, and the formation of capillary-like structures from primary cultured human umbilical vascular endothelial cells in a dose-dependent manner. In addition, AKBA suppressed VEGF-induced phosphorylation of VEGF receptor 2 (VEGFR2) kinase (KDR/Flk-1), Src family kinase, and focal adhesion kinase. These findings suggest that AKBA potently inhibits human prostate tumor growth through inhibition of angiogenesis induced by VEGFR2 signaling pathways (Pang *et al*., 2009).

In another study, the tetracyclic tirucallic acids from the oleogum resin of *Boswellia carteri* especially 3-á-acetoxy-tirucallic acid and 3-â-acetoxy-tirucallic acid inhibited cell proliferation and induce apoptosis on prostate cancer cells *in vivo* in chick chorioallantoic membrane xenografts and reduced prostate tumor growth in nude mice implanted with human PC-3 prostate cancer cells (Estrada *et al*., 2010). It has been found that these compounds act mainly on suppression of Akt signaling, and they represent a new class of Akt inhibitors (Estrada *et al*., 2010).

Leukemia

Jing *et al*. showed that boswellic acid acetate (BAA) isolated from *Boswellia carteri*, induced monocytic differentiation of myeloid leukemia HL-60, U937 and ML-1 cells with 90% of the cells showing morphologic changes (Jing *et al*., 1999). Specific and non-specific esterases were also increased by BAA. In contrast to its selective differentiation effect, BAA strongly inhibited growth of all cell lines tested which was dose- and time-dependent. In addition to induction of differentiation, BAA caused morphologic changes and DNA fragmentation indicating induction of HL-60 cell apoptosis (Jing *et al*., 1999).

Similarly, BA, ABA, KBA, and AKBA were examined for their *in vitro* antitumor activity (Shao *et al*., 1998; Huang *et al*., 2000). These compounds inhibited the synthesis of DNA, RNA and protein in human leukemia HL-60 cells in a dose-dependent manner, and AKBA showed the most pronounced inhibitory effects on DNA, RNA and protein synthesis with IC_{50} values of in the nM range (Shao *et al*., 1998; Huang *et al*., 2000).

Moreover, the ethanolic extract of *Boswellia serrata* gum resin containing a defined amount of boswellic acids was tested for its cytotoxic, cytostatic and apoptotic activity on five leukemia (HL-60, K 562, U937, MOLT-4, THP-1) cell lines by WST-1 assay and flow cytometry (Hostanska *et al*., 2002). The *Boswellia serrata* extract induced dose-dependent antiproliferative effects on all human malignant cells tested. In three different haematological cell lines (K562, U937, MOLT-4) the effect of total extract was about 3-fold more potent than pure AKBA. Morphological changes, annexinV-binding and propidium iodide-labeled staining confirmed induction of apoptosis by the treatment. The results of this study suggest the effectiveness of *Boswellia serrata* extract with defined content of boswellic acids (Hostanska *et al*., 2002).

It has been also shown that a pentacyclic triterpenediol (TPD) obtained from *Boswellia serrata*, which exists in nature as an isomeric mixture of 3α, 24-dihydroxyurs-12-ene and 3α, 24-dihydroxyolean-12-ene, cause cell death in human leukemia HL-60 cells (Bhushan *et al*., 2007). TPD caused apoptosis as shown by increasing sub-G_0 DNA fraction, induce DNA ladder fragmentation and enhance annexin V-FITC binding of the cells. Furthermore, it caused a large increase in reactive oxygen species and nitric oxide production. It also leads to loss of mitochondria membrane potential and release of cytochrome c, AIF, Smac/DIABLO to the cytosol. In addition, TPD up-regulated the expression of the cell death receptors DR4 and TNF-R1 and a corresponding increase in caspase-8 activation. This study suggests that TPD produces oxidative stress in cancer cells that triggers self destruction by ROS and NO regulated activation of both the intrinsic and extrinsic signaling cascades (Bhushan *et al*., 2007).

Brain Cancer (Glioma)

Glaser and coworkers have reported that boswellic acids induce apoptosis in human malignant glioma cells (LN-18, LN-229, LN-308 and T98G) (Glaser *et al*., 1999). It has been found that AKBA-induced

apoptosis does not involve the generation of reactive oxygen species; however, AKBA activated p21 expression suggesting a role for p21 as an effector of AKBA-induced apoptosis. Interestingly, p21 has been found to accumulate in gliomas *in vivo,* and p21 has crucial role in inhibiting drug-induced apoptosis in glial and non-glial tumor cells (Jung *et al.*, 1995; Sheikh *et al*., 1997; Ruan *et al*., 1998) and it mediates the cytoprotective effects of steroids in glioma cells (Naumann *et al.*, 1998). In addition, boswellic acids synergize with the cytotoxic cytokine, CD95 ligand (which is a novel target for malignant glioma therapy), in inducing glioma cell apoptosis (Glaser *et al*., 1999).

In another study, female Wistar rats were treated with an extract from gum resin of *Boswellia* for 14 days after inoculation of C6 tumor cells into their right caudate nucleus (Winking *et al*., 2000). Results have showed that survival time of the rats in the highest dosage group was more than twice as long as in the control group. Histological examination of brains obtained from animals in this study showed that the proportion of apoptotic tumor cells animals in the treatment group was significantly larger than in control group. These data demonstrate an influence of *Boswellia* gum resin extract on rat glioma growth and it might represent a new therapeutic option for glioma treatment in future (Winking *et al*., 2000).

Patients irradiated for brain tumors often suffer from cerebral edema and as a result are often treated with dexamethasone to inhibit inflammation following radiation exposure (Kirste *et al.,* 2011). In a human clinical study, an extract from *Boswellia serrata* resin has been shown to reduce cerebral edema, as measured by MRI, in patients with primary or secondary malignant cerebral edema (Kirste *et al*., 2011). Both AKBA and KBA were detected in patients' serum. These results indicate that boswellic acids might be used as an alternative to dexamethasone treatment in patients receiving brain irradiation (Kirste *et al.*, 2011).

Colorectal Carcinoma

Huang and coworkers have found that feeding 0.2% of the methanolic extract of gum resin of *Boswellia serrata* in the diet to mice for six weeks inhibited azoxymethane (AOM)-induced formation of aberrant crypt foci in colon epithelium of mice by almost 50% (Huang *et al.*, 2000). In other studies, the antiproliferative and apoptotic effects of BA, KBA and AKBA were examine in HT-29 colon cancer cells (Liu *et al*., 2002). Results showed that KBA and AKBA increased cytoplasmic DNA-

histone complex and increased sub-G_0 HT-29 cell population indicating induction of cell death, and AKBA effects were superior to KBA. Both compounds increased caspase-8, caspase-9 and caspase-3 activities accompanied by cleavage of PARP. The apoptosis induced by AKBA was inhibited completely by caspase-3 or caspase-8 inhibitor and partially by caspase-9 inhibitor. Apart from apoptotic effect, these acids also inhibited H^3-thymidine incorporation and cell viability to different extent (Liu *et al*., 2002).

In a recent study, the effect of AKBA on colon cancer cell line HT29 in the absence or presence of LY294002 or wortmanin (inhibitors of PI3K) was investigated (Liu and Duan, 2009). Results of this study have showed that AKBA treatment induced apoptosis of these cells; however, pre-incubation of these cells with LY294002 or wortmannin significantly enhanced the AKBA-induced apoptosis up to 20-fold. Furthermore, combined LY294002 or wortmannin and AKBA treatment leads to drastic inhibition of Akt phosphorylation at both Ser473 and Thr308 positions (Liu & Duan, 2009).

Yadav *et al*. showed that oral administration of AKBA inhibited the growth of tumors in mice implanted orthotopically with human colorectal carcinoma cell line HCT116 in a dose-dependent manner, and a decrease in tumor volumes, ascites and distant metastasis to the liver, lungs and spleen in implanted tumors in nude mice (Yadav *et al*., 2012). Tumor proliferation index Ki-67 and microvessel density marker CD31 were significantly down-regulated by AKBA treatment. In addition, AKBA treatment significantly suppressed NFκB activation, COX-2, Bcl-2, cyclin D1, MMP-9 and VEGF expression in the tumor tissue. HPLC analysis of serum and tumor tissues has shown a dose-dependent increase in the levels of AKBA was detected, indicating its bioavailability. These findings suggest that AKBA, a boswellic acid analog, can suppress the growth and metastasis of human colorectal carcinoma *in vivo* (Yadav *et al*., 2012).

It has been found that AKBA significantly up-regulated expression of the let-7 and miR-200, which are tumor suppressing miRNAs, in various colorectal carcinoma cell lines (Takahashi *et al.,* 2012). In addition, AKBA modulated the expression of several downstream targets of the let-7 and miR-200, such as CDK6, vimentin and E-cadherin. These data were further confirmed by miRNA knockdown studies that revealed that inhibition of let-7i facilitated enhanced cancer cell proliferation, migration and invasion. In addition, AKBA also induced similar modulation of the let-7 and miR-200 downstream genes in colorectal

carcinoma tumors orthotopically implanted in nude mice. These results indicate that boswellic acids can regulate cellular epigenetic machinery in colon cancer (Takahashi *et al*., 2012).

Bladder Cancer

In a study investigating the effects of commercial frankincense oil on both normal and bladder cancer cells, it has been found that frankincense oil suppressed cell viability in human bladder carcinoma J82 cells, but did not affect cell viability in immortalized normal urothelial UROtsa cells (Frank *et al*., 2009). Microarray analysis has supported patterns of stress, activation of cell cycle arrest, suppression of cell proliferation, and activation of apoptotic signaling in frankincense oil-treated J82 cells within 1 hour of treatment exposure (Frank *et al*., 2009).

Skin Cancer

A report by Huang *et al.* showed that topical application of a methanolic extract of the gum resin exudate of *Boswellia serrata*, which contains â-boswellic acid and its structural related derivatives, to the backs of mice markedly inhibited 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced increases in skin inflammation, epidermal proliferation, the number of epidermal cell layers, and tumor promotion in 7,12-dimethylbenz[a]anthracene (DMBA)-initiated mice (Huang *et al*., 2000).

Additional studies performed to investigate the antitumor effect of α and β-boswellic acid acetate (BAA), which is an isomeric compound, isolated from the plant *Boswellia carteri* (Zhao *et al*., 2003). BAA treatment caused cytotoxic activity and induced the differentiation of B16F10 mouse melanoma cells. In addition, BAA blocked the cell population in G1 phase and inhibited topoisomerase II activity in these cells. Furthermore, BAA inhibited the migration activity of B16F10 melanoma cells and the secretion of MMPs from HT-1080 fibrosarcoma cells (Zhao *et al*., 2003).

Hepatocellular Carcinoma

Investigators have also shown that BA, KBA and/or AKBA treatment on cultured human liver cancer Hep G2 cells induced potent antiproliferative and apoptotic effects (Liu *et al*., 2002). Boswellic acids decreased cell viability as shown by a reduction in H^3-thymidine

incorporation and cell cycle arrest in G_0/G_1 phase. Moreover, boswellic acids strongly induced apoptosis accompanied by activation of caspase-3, -8 and -9 and increasing the percentage of sub-G_1 cells. Apoptosis by these agents was blocked completely when given in combination with caspase-8 or caspase-3 inhibitors, while only slightly inhibited when given in combination with a caspase-9 inhibitor (Liu *et al*., 2002). These findings suggests that boswellic acid induced apoptosis in these cells is mediated through death receptor-dependent caspase-8 activation.

CONCLUSIONS

Taken together, results obtain from a wide range of investigations demonstrates that various compounds isolated from *Boswellia* essential oil possess antiproliferative, proapoptotic, antimigratory, and antiangiogenic activities against a wide range of cancer cell types. Cell culture, pre-clinical and clinical studies have also demonstrated that AKBA, a triterpenoid isolated from *Boswellia* species, shows great potential for use as an anticancer agent.

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