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Role of Boswellic Acids in Cancer Treatment

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Cancer is perceived as a disease of unregulated communication within cells of the body. Currently chemotherapy, radiation therapy, immunotherapy, photodynamic therapy, hormonal therapy and surgery have been used for cancer treatment. The therapeutic success rate for cancer can be tremendously improved by use of natural products such as *Catharanthus roseus*, *Curcuma longa*, *Taxus bravifolia*, *Camptotheca acuminata* etc. Boswellic acids are bioactive pentacyclic triterpenes derived from natural plant source (*Boswellia serrata*) represents one of the most promising anticancer agent. Various anticancer research studies and published data reported on safety of *Boswellia serrata* showed that boswellic acids can be used for treatment of colon cancer, pancreatic cancer, brain tumor, leukemia and prostate cancer etc. An attempt has been made in this review to highlight the treatment therapies, different *Boswellia* species, structural composition and role of boswellic acids in cancer therapy, safety/toxicological profile and interactions of boswellic acids.

Key words: Cancer therapies, *Boswellia* species, boswellic acids, cell lines

INTRODUCTION

Cancer disease is still increasing worldwide in spite of advances for diagnosis and its treatment (Murthy and Mathew, 2004). Cancer is cohort of diseases characterized by an abnormal and anarchical cell proliferation within a normal tissue of the body disregarding the normal rules of the cell division (Huang *et al.*, 2012). It has been reported that (American Cancer Society) the probability for development of cancer during one's lifetime is one in two for men and one in three for women. Cancer affects millions of persons in all age groups. Intense research has led to a more comprehensive understanding of cancer at the genetic, molecular and cellular levels providing an avenue for methods of increasing antitumor efficacy of drugs while reducing systemic side effects. Effective current treatments for various cancers include chemotherapy, radiation, photodynamic therapy, hormone therapy and surgery (Bharali *et al.*, 2009; Praetorius and Mandal, 2007; Kilicay *et al.*, 2011; Cho *et al.*, 2008; Wong *et al.*, 2007; Serpe, 2006; Chemotherapy treatment-<http://www.cancer.org/acs/groups/cid/documents/webcontent/002995-pdf.pdf>).

Different therapies being employed for the treatment of cancer are tabulated in Table 1. An attempt is made in this manuscript to summarize the role of boswellic acids (BAs) for the treatment of cancer. Further, the structural aspects, research studies on BAs, interaction, safety and toxicity are highlighted.

Herbal medicines which formed the basis of health care throughout the world are still widely used and natural products continue to play an important role in the discovery and development of new pharmaceuticals, as clinically useful drugs, as well as starting materials to produce synthetic drugs (Zhang, 2013; Topliss *et al.*, 2002). Natural products have provided the most important successes in the chemotherapy for cancer treatment (Qurishi *et al.*, 2010).

Currently, various plant based anticancer drugs are under development that target signalling as well as epigenetic pathways that can cause cancer. A large number of anticancer drugs are unmodified natural products obtained from plants or microorganisms, which includes important anticancer drugs-bleomycin, doxorubicin, daunorubicin, vincristine, vinblastine, mitomycin, streptozocin and paclitaxel (Taxol™). Irinotecan (acamptothecin derivative), etoposide and tenoposide (podophyllotoxin derivatives) are examples of semisynthetic derivatives of natural products that are important anticancer drugs. Vincristine and vinblastine are complex, dimeric indole-indolines obtained from *Catharansus rosea* and are most important drugs used in chemotherapy for the treatment of cancer (Loo and Freireich, 1995; Tyler *et al.*, 1988; Feng *et al.*, 2011).

The search for new anticancer drugs from plants would be a fruitful frontier in cancer treatment and chemoprevention (Qurishi *et al.*, 2010). Frankincense, also known as Olibanum is an oleogum resin produced by a group of trees belonging to the genus *Boswellia* of family Burseraceae. The genus *Boswellia* named after Johann Boswell and has approximately 20 species, occurring in the dry regions spanning from West Africa to Arabia and South to the Northeast region of Tanzania. In addition, its species have been found in India and Madagascar (Van Vuuren *et al.*, 2010; Hussain *et al.*, 2013; Paul, 2012). The resin is obtained by making scrapes in the trunk of the *Boswellia* species and collecting the dried resin gums from the trees later. Olibanum is produced mainly by following species depending on the geographical location (Hamidpour *et al.*, 2013).

Boswellia sacra Flueck (found in Southern Arabia) is a tree indigenous to Dhofar region and is one of the most famous plants of Sultanate of Oman. It is also known as "Luban dhakar" or Kendar in Arabic region. The oleo-gum resin of *B. sacra* is an economically as well as culturally important product of Oman (Al-Saidi *et al.*, 2012; Sabra and Al-Masoudi, 2014).

Boswellia carterii Birdw (found in Somalia and Southern Arabia) is better known as "Mohr". This species is also found in Sudan and in rare cases in Yemen. *Boswellia carterii* and *B. sacra* olibanum have quite similar chemical compositions and are characterized by the presence of lupeolic acid (Wang *et al.*, 2011; Zhang *et al.*, 2013).

Boswellia frereana Birdw (found in Somalia) produces the most expensive type of olibanum on the market and resin produced by this species is known as "Loban majdi" or more commonly, as "Maydi". *Boswellia frereana* is characterized by the presence of lupeol and 3-epi-lupeol in conjunction with triterpenes skeletons. Lupeolic acid, BAs and their respective O-derivatives are not found in frankincense produced from these species (Zhang *et al.*, 2013).

Boswellia papyrifera Hochst (found in East Africa) is another deciduous, gum-producing, multipurpose perennial tree that grows in Somalia, Ethiopia, Eritrea and in the other East African countries is claimed to have been the source of olibanum and produces resin of a quality known as "Boido" (Dekebo *et al.*, 1999; Assefa *et al.*, 2012).

Boswellia serrata Roxb (found in East India) is also known as "Indian olibanum" and is found in the central and northern parts of East India especially dry hilly forests of Rajasthan, Madhya Pradesh, Gujrat and Bihar etc. This species produces olibanum resins of various qualities, which are commonly known as "Salai guggul, White guggul or Indian olibanum or Kundur".

Table 1: Different therapies used for treatment of cancer

Therapy	Agents used	Examples	Mechanism	Cancer type	Reference
Chemotherapy	Cell destroying drugs	Alkylating agents, antimetabolites and antitumor antibiotics	Cell cycle arrest	Multiple metastases and leukemias	Natalie and Mandal (2007)
Radiation therapy	Radiations	X-rays, gamma-rays	Apoptosis, necrosis, autophagy	Skin cancer, prostate cancer, lung carcinoma	Baskar <i>et al.</i> (2012); Understanding radiation therapy: A guide for patients and families at http://www.cancer.org/acs/groups/cid/documents/webcontent/003028-pdf.pdf
Immuno-therapy	Immune system stimulating agents	Monoclonal antibodies, cancer vaccines	Immune system stimulation or by increasing tumor cells immunogenicity	Breast, colon, kidney, lung and prostate, as well as leukemia, lymphoma	Natalie and Mandal (2007), Disis, www.meds.com/immunotherapy/tumor_immunology.html
Photodynamic therapy	Photosensitizer	Porfimer sodium, Verteporfin	Photooxidation	Early bladder tumor, early lung and esophageal cancer	Calin and Parasca (2006)
Hormonal therapy	Specific hormones	Prostap, Zoladex	By altering the production or activity of particular hormone	Breast and prostate cancer	(Hormonal therapies at http://www.macmillan.org.uk/Cancerinformation/Cancertreatment/Treatmenttypes/Hormonaltherapies/Hormonaltherapies.aspx)
Surgery	Surgical procedures	Prophylactic surgery, diagnostic surgery, staging and curative surgery	Cancer cells and tumor are removed by surgeon	Colorectal, ovarian, prostate and breast cancer	(Surgical oncology, http://en.wikipedia.org/wiki/Surgical_oncology , Surgery for prostate cancer, http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-treating-surgery)

Boswellia serrata is characterized by the presence of tirucallane and euphane skeletons, which are not commonly found in other *Boswellia* species, in addition to BAs and their respective O-acetyl derivatives. The oleogum resin of *B. serrata* have become more and more popular for the treatment of various diseases such as cancer, arthritis, inflammation, asthma and hypolipidemia etc. (Zhang *et al.*, 2013; Alam *et al.*, 2012; Siddiqui, 2011; Siddiqui *et al.*, 1984; Eichhorn *et al.*, 2011; Shah *et al.*, 2008; Ammon, 2006).

Boswellia serrata gum resin contains 8-12% essential oils, 45-60% polysaccharides, 25-35% higher terpenoids, sugars and compromises of proteins and inorganic compounds. It contains essential oil which is a mixture of monoterpenes (α -thugene) diterpenes (macrocyclic diterpenoids such as incensole, incensole oxide, iso- incensole oxide and triterpenes (α and β amyrins). Moreover, phenolic compounds, a diterpene alcohol (serratol) is also found in essential oil (Shah *et al.*, 2009; Sharma *et al.*, 2009). The exploration for active moieties in the gum resin further led to the isolation of BAs that belong to the ursane and oleanane type pentacyclic triterpenes. Higher terpenoids constitute the major fraction (25-35%) of the oleogum resin which are pentacyclic triterpenic acids known as boswellic acid such as β -boswellic acid (53.5-246.9 mg g⁻¹), 11-keto-boswellic acid (4.48-5.81 mg g⁻¹), 3-O-acetyl- β -boswellic acid (38.4-192.9 mg g⁻¹) and 3-O-acetyl-11-keto- β -boswellic acid (32.7-44.2 mg g⁻¹). The major chemical constituents of *Boswellia serrata* are BAs and structures of four BAs as shown in Fig. 1. From structure activity relationship studies, it has been indicated that pentacyclic ring skeleton of BA is important for anti-topoisomerase activity (Qurishi *et al.*, 2010; Bhushan *et al.*, 2007; Upaganlawar and Ghule, 2009; Simmet and Ammon, 2001; Qazi *et al.*, 2009; Sharma *et al.*, 2010).

ANTICANCER ACTIVITIES ON BAS

Various studies have showed that BAs significantly inhibit various cancerous cell lines which can play an important role for treatment of cancer disease as represented in Table 2.

Anticancer research studies on human cancer cell lines: Liu and Duan investigated the effect of 3-acetyl-11-keto- β Boswellic Acid (AKBA) on colon cancer cells by initiating the apoptosis (programmed cell death) in HT29 Colon cancer cells in the absence and also in the presence of LY294002 (selective phosphatidylinositol 3-kinase inhibitor). Estimation of apoptosis was performed via flow cytometry and caspase assay on cell lines. It was found that AKBA only slightly induced apoptosis at 30 μ M but AKBA-induced apoptosis was significantly enhanced up to 20-fold by pre-incubation of the cells with LY294002 or wortmannin (Liu and Duan, 2009). Further, Liu *et al.* (2006) explored that AKBA inhibits the cellular growth in different colon cancer cells by G1 phase arrest after AKBA treatment.

Cellular growth inhibitory effect of AKBA was examined by flow cytometry cell cycle analysis and western blot analysis (Liu *et al.*, 2006). Hoernlein *et al.* (1999) investigated the cellular growth inhibition effect of AKBA on leukemic cell, proliferation of HL-60 cell lines and revealed that cells undergo apoptosis (confirmed with the help of flow cytometric analysis) cell counts and thymidine incorporation were considerably reduced by AKBA concentration.

The inhibitory effect of AKBA was investigated by Yuan *et al.* (2008) on prostate cancer cells lines. Androgen receptor mediated signalling is crucial for development and progression of prostate cancer. The AKBA mediated inhibition of cellular proliferation was associated with decrease of androgen receptor expression

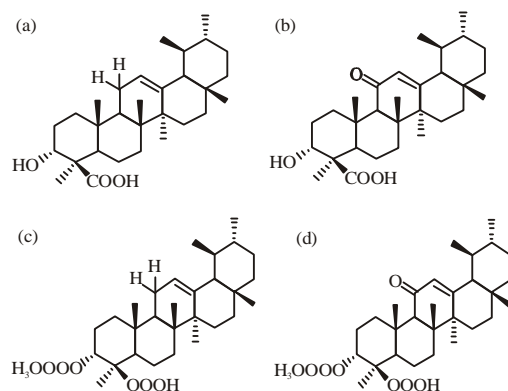


Fig. 1(a-d): Structure of four different Boswellic acids, (a) β -Boswellic acid, (b) 11-Keto- β -Boswellic acid, (c) Acetylc- β -Boswellic acids and (d) Acetyl-11 Keto- β -Boswellic acids

which was confirmed by Electrophoretic mobility shift assay and Transient transfection assay (Yuan *et al.*, 2008). The effect of BAs on leukemic and brain tumor cell lines for its cytotoxic and apoptotic effect was evaluated by Hostanska *et al.* (2002). Morphological changes after 24-27 h and the detection of apoptotic cells by AnnexinV-binding and/or by the detection of propidium iodide-labelled DNA with flow cytometry were observed and confirmed the apoptotic cell death (Hostanska *et al.*, 2002). Saraswati and Aggrawal (2012) evaluated the boswellic acid as a potent anticancer agent against MCF-7 breast cancer cell lines. Effects were studied against multiple intracellular targets that affect angiogenesis (VEGF), inflammation (TNF- α , IL-12) and apoptosis (caspase-3 and -9). It was observed that BA inhibits MCF-7 cell proliferation and potentiates the cell death (Saraswati and Agrawal, 2012). Moreover, Jing *et al.* (1999) found that a compound extracted from the herbs of *Boswellia* species can cause differentiation and apoptosis of leukemia cells. It was found that BA acetate induced monocytic differentiation of myeloid leukemia cells. The apoptotic and differentiation effects of BA acetate suggested that it may be a powerful agent in the treatment of leukemia (Jing *et al.*, 1999).

Xia *et al.* (2005) studied the cytotoxic effect of BA acetate, which consists of 1:1 mixture of both alpha-BA acetate and beta-BA acetate on different myeloid leukemia cells lines. Study of morphologic and DNA fragmentation assays showed that the cytotoxic effect of BA acetate was mediated by initiation of apoptosis pathway (Xia *et al.*, 2005). The apoptotic effects of AKBA in human prostate cancer cells with the activation of caspase-3 and caspase-8 as well as with poly (ADP) ribose polymerase (PARP) cleavage was investigated by Lu *et al.* (2008).

Anticancer research findings on both human cancer as well as on animal cell lines: Zhao *et al.* (2003) studied the antitumor effect of BA acetate-4 by MTT (3-(4,5-dimethylthiazol-2-yl), 2,5-diphenyltetrazolium bromide) assay, time-lapse video microscopy and computer-assisted cell tracking for estimation of tumor cells migration within a three-dimensional collagen matrix. Mouse melanoma cells were used for topoisomerase II isolation and its activity was determined by its ability to cut plasmid pBR322 DNA. The results showed that BA acetate-4 induced the differentiation in mouse melanoma cells, blocked cell growth at G1 phase of cell cycle and topoisomerase II activity was also inhibited (Zhao *et al.*, 2003). Uthaman *et al.* (2012) explored the cytotoxic effect of *Boswellia serrata* extract against different A375, MIA-PaCa, mouse melanoma and human pancreatic cancer cell line. In order to understand the mechanism of action, DNA fragmentation assay was

done and the results showed that the extract had the potential to fragment the DNA which is the hall mark of apoptosis (Uthaman *et al.*, 2012).

Anticancer research studies on both human cancer cell lines as well as on animal model: Park *et al.* (2011) observed AKBA induced cellular proliferation inhibition on four different cancer cell lines (AsPc-1, BxPC-3, MIA PaCa-2 and PANC-28). Anti-proliferative effect of AKBA was further evaluated by *in-vitro* model in an orthotopic nude mouse model of pancreatic cancer and concluded that administration of AKBA (100 mg kg⁻¹) significantly inhibited the cell proliferation (Park *et al.*, 2011). Takahashi *et al.* (2012) hypothesized that AKBA may exert their chemo-preventive effects by modulating specific microRNA (miRNA) pathways such as let-7 and miR-200 families that contain tumor suppressive miRNAs which was found to be involved in pathogenesis of human cancer. They found that AKBA significantly up-regulated the expression of let-7 and miR-200 families in colorectal cell lines and on the basis of immunohistochemistry, colony formation assay, migration and invasion assay. The miRNA knockdown studies and AKBA induced modulation of let-7 and miR-200 in orthotopically implanted colorectal tumor in nude mice were also conducted and concluded that both let-7 and miR-200 are putative tumor suppressive miRNAs (Takahashi *et al.*, 2012). Yadav *et al.* (2012) observed that oral administration of AKBA (50-200 mg kg⁻¹) inhibited the growth and metastasis of colorectal cancer in orthotopically implanted tumor in nude mice. They found that AKBA dose dependently inhibited the growth of tumor in mice, resulting in decrease in tumor size than those seen in vehicle treated mice without significant decrease in body weight (Yadav *et al.*, 2012) (Table 2).

Safety aspects of Boswellic acids: Kimmatkar *et al.* (2003) conducted a randomized double-blind, placebo-controlled cross-over study to assess the safety and efficacy of *B. serrata* extract in osteoarthritis of the knee in 30 patients. Fifteen patients received the active *B. serrata* extract or placebo for 8 weeks. Subsequent to the first treatment, a washout period was allowed and the groups were then crossed over to receive the opposite intervention for 8 weeks. It was found that all patients receiving *B. serrata* extract showed a decrease in knee pain, increased walking distance and increased knee flexion. Observed differences between placebo and drug treatment were statistically significant (p<0.05) (Kimmatkar *et al.*, 2003).

Singh *et al.* (2012) conducted the assessment of the safety potential of *B. serrata* extract. A repeated oral dose for 90 days was given to find out the toxicity data of *B. serrata* using 10 rats of each sex. Rats were treated at

Table 2: Anticancer research studies on cell lines and animal models

Boswellic acid	Cancer type	Cell lines	Analysis	Reference
Anticancer studies on human cancer cell lines				
AKBA	Colon cancer	HT-29, HCT-116	Flow cytometry, cell viability and DNA synthesis assay, western blot analysis, apoptosis assay	Liu and Duan (2009)
AKBA	Colon cancer	HT-29	ELISA, flow cytometry, Assay activities of caspase-3, caspase-8 and caspase-9, cell viability and DNA synthesis, western blot analysis	Liu <i>et al.</i> (2006)
AKBA	Leukemia	HL-60, CCRF-CEM	Flow cytometry, topoisomerase activity analysis, cDNA polymerase chain reaction approach	Hoerlein <i>et al.</i> (1999)
AKBA	Prostate cancer	LNCaP	Flow cytometry, MTT assay, Transient transfection assay, western blot analysis, Electrophoretic mobility shift assay	Yuan <i>et al.</i> (2008)
BSE	Leukemia, brain tumor	Five leukemia (HL-60, K 562, U937, MOLT-4, THP-1 and two brain tumor (LN-18, LN-229	WST-1 assay and flow cytometry	Hostanska <i>et al.</i> (2002)
BA	Breast cancer	MCF-7	Caspase activity assay, cytokine ELISA assay, superoxide dismutase activity, catalase activity, glutathione assay	Saraswati and Aggrawal (2012)
BAA	Leukemia	ML-1, HL-60, U937, K562	DNA fragmentation analysis, phase microscopy	Jing <i>et al.</i> (1999)
BAA	Leukemia	NB4, SKNO-1, K562, U937, ML-1 and HL-60	Clonogenic assay, mitochondria membrane potential assay, western blot analysis, northern blot analysis	Xia <i>et al.</i> (2005)
AKBA	Prostate cancer	PC-3, LNCaP	MTT proliferation assay, mitochondria membrane potential analysis, luciferase assay	Lu <i>et al.</i> (2008)
Anticancer research findings on both human cancer as well as on animal cell lines				
BAA	Metastatic Melanoma, fibrosarcoma	Mouse melanoma cells B16F10 and human fibrosarcoma cell line HT-1080	MTT proliferation assay, cell viability analysis, gelatin zymography, topoisomerase-II catalytic assay, flow cytometry and DNA fragmentation	Zhao <i>et al.</i> (2003)
BSE	Pancreatic and melanoma	Human MIA-PaCa, A375 and mouse fibroblast cell line L929	MTT proliferation assay, DNA fragmentation assay	Uthaman <i>et al.</i> (2012)
Anticancer research studies on both human cancer cell lines as well as on animal model				
AKBA	Pancreatic cancer	ASP-1, BxPC-3, MIA PaCa-2, PANC-28, Orthotopic mouse model	MTT proliferation assay, western blot analysis and immunohistochemical analysis	Park <i>et al.</i> (2011)
AKBA	Colorectal cancer	HCT116, HT29, SW480 and SW620, Orthotopic mouse model	MTT proliferation assay, immunohistochemistry, colony formation assay, migration and invasion assay	Takahashi <i>et al.</i> (2012)
AKBA	Colorectal cancer	Orthotopic mouse model	Proliferative index, nuclear factor- κ B (NF- κ B) suppression	Yadav <i>et al.</i> (2012)

^aAKBA: 3-acetyl-11-keto- β boswellic acid, ^bBSE: *Boswellia serrata* extract, ^cBA: Boswellic acid, ^dBAA: α - and β -Boswellic acid acetate, ^eELISA: Enzyme Linked Immunosorbent Assay, ^fMTT: [3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide], ^gWST: Water soluble tetrazolium salt

three different doses i.e., 100, 500 and 1000 mg kg⁻¹ b.wt. with the *B. serrata*. Ten rats of each sex were treated with corn oil only, which was the vehicle as a control. Two groups consisting of five male and five female rats were kept as control recovery and high dose recovery group which were treated with the vehicle (corn oil) and the *Boswellia serrata* at the dose of 1000 mg kg⁻¹ b.wt. Without any treatment animals of control recovery and high dose recovery groups were observed for 28 days. It was concluded from the results that *B. serrata* is relatively safe in rat up to the dose of 500 mg kg⁻¹ b.wt. as no adverse impact on health factors (Singh *et al.*, 2012).

Krishnaraju *et al.* (2010) studied Aflapin a novel synergistic composition derived from *B. serrata* gum resin. Acute and sub-acute toxicity studies were carried out in different animal models to assess the safety of Aflapin. Initially dermal irritation study was done by using Newzealand white rabbits indicated that Aflapin is non-irritating to skin. Aflapin caused minimal ocular irritation in a primary eye irritation test conducted on Newzealand Albino rabbits. A repeated dose 28 days sub-acute oral toxicity study in Sprague Dawley rats confirmed no significant signs of toxicity. Different evaluation studies including hematology, clinical chemistry, gross necropsy and histopathology did not show any significant adverse changes (Krishnaraju *et al.*, 2010).

Interactions/synergistic effects of *B. serrata*:

Sferra *et al.* (2012) studied the effects of a combined therapy with anti-fibrotic *Salvia* and anti-inflammatory *Boswellia* extracts on chronic hepatitis-associated fibrosis induced by Dimethylnitrosamine (DMN) in mice by intra peritoneal, as well as on the hepatic expression of TGF-beta1 and Smad proteins. Mice were divided into five groups: Controls, DMN without any treatment, DMN treated orally with *Boswellia* extracts (50 mg kg⁻¹ day⁻¹), DMN treated orally with *Salvia* extracts (150 mg kg⁻¹ day⁻¹), DMN treated orally with both *Salvia* extracts (150 mg kg⁻¹ day⁻¹) and *Boswellia* (50 mg kg⁻¹ day⁻¹). Histological and immunohistochemical analysis was done by macroscopic examination on excised liver. The combined oral administration of *Boswellia* and *Salvia* extracts improved the course and macroscopic findings of DMN-induced chronic hepatitis-associated fibrosis (Sferra *et al.*, 2012).

Tripathi (2009) studied the BHUx is a five-herb combination formula consisting of *B. serrata*, *Terminalia arjuna*, *Strychnos nux vomica*, *Commiphora mukul* and *Semecarpus anacardium* found to be effective in treating arterosclerosis and hyperlipidemia. The antioxidant, anti-inflammatory, hypo-lipidemic, anti-proliferative properties of BHUx on several experimental models based on chemical tests, cell culture, *in vitro* models and *in vivo* experiments with

normal and transgenic animals was studied. A separate pre-clinical toxicity study was also carried out to prove its safety margin in therapeutic doses (Tripathi, 2009).

CONCLUSION

Currently, there is need for compounds that target multiple molecular and cellular pathways in cancer with lesser side effects. It is apparent that natural products have considerably less side effects and BAs obtained from natural source displays those traits in cell lines as well as on animal models. Different species of *Boswellia* produces potential metabolites especially Boswellic acids that have generated extensive interest due to various beneficial pharmacological properties and effective remedy for the complementary treatment of cancer diseases. Clinical trials are on the way to focus the effects of boswellic acids. As far as chemoprevention, safety and toxicity is considered, administration of boswellic acids is relatively safe and may have long term anticancer effects.

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