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REVIEW ARTICLE

Frankincense: A potential phytotherapeutic agent in cancer treatment

Foziya Khan, Luay Rashan*, Adeeb Shehzad & Atiya Fatima

Biodiversity Unit, Dhofar University, Salalah 211, Oman

*Correspondence email - lrashan@du.edu.om

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Abstract

Plant-isolated compounds are the roadmap for the modern pharmaceutical industry due to the anticancer activities of their bioactive constituents and metabolites. *Boswellia sacra* (Burseraceae) oleo gum resin has cytotoxic potential for the cure of various ailments, including infectious, inflammatory and arthritic diseases. Cancer is a complex health condition characterized by gene mutation and increased cell number. Worldwide, cancer is regarded as the most critical reason for morbidity and mortality. Traditional Chinese medicine, Ayurveda and Arab folk medicine all utilized it as an anticoagulant, antimicrobial, immunomodulatory and antidiabetic agent. Boswellic acids (BA), an active component of frankincense isolated from the dried gum resin of *B. sacra* has been utilized for the cure of several ailments, including inflammatory diseases, cancer, cerebral edema, asthma, chronic pain syndrome, arthritis, memory disorders and chronic bowel diseases since years. This study was designed to summarize the recent scientific knowledge regarding the anti-cancer properties of Frankincense (Olibanum), which is obtained from the *B. sacra.* However, further studies are required to elucidate its exact underlying molecular mechanisms in cancer treatment. Frankincense's ability to reduce inflammation is mediated by inhibitionof several pathways like LOX, COX-2 pathway and downregulation of CXCR4, VEGF, NF-κB and matrix metalloproteinases MMPs. BA also displayed an anti-proliferative effect and induced apoptosis in several cancer cells, such as HCT-116 and MCF-7 cells. AKBA (3-O-acetyl-11-keto-β-boswellic acid) has been shown to activate extrinsic apoptotic pathways by causing the cleavage of procaspases and PARP and to inhibit the Wnt/β-catenin, PI3K/AKT and EGFR pathways, while activating the ATM/P53 signaling pathway. The therapeutic potential and anticancer properties of frankincense are still in the early stages of investigation. This review summarizes the efficacy of BA in various types of cancer and provides a wide scope of study on the anti-cancer properties of BA in terms of the development of novel drugs that would be more helpful both physically and economically.

Keywords: anti-inflammatory; boswellic acid; cancer; cell death; frankincense

Introduction

Frankincense is known in French as "pure incense," highlighting its traditional use as a fragrant and aromatic substance. Salai Guggal, Kundur, Indian Olibanum and Loban are some of its common names. Traditionally, in religious, cultural rites and social celebrations, it has been used for incense and fumigation and for treating several types of illnesses (1). Native to tropical regions, *Boswellia* trees are deciduous plants that typically grow as small shrubs or trees, producing oleogum resins (2). To fulfill the global need, the cultivation of trees has been expanded (3). To obtain the resin, incisions are made in the tree trunks, allowing the gum to flow from the wounded ducts before being collected once dried (1, 4). Usually, *Boswellia* tree produces high-quality resin after the initial 3 years of harvesting; it requires recovery time; subsequent harvests will provide resin of significantly lower grade (5).

Traditionally, *B. sacra* resin has been used to alleviate a broad range of symptoms, including inflammatory and cancer conditions (6). BA is pentacyclic triterpenic acids, which is an active component of frankincense and primarily responsible for its anti-inflammatory effect (7). Although BA shares structural similarities with steroids, but anti-inflammatory effects through inhibition of 5-lipoxygenase, have demonstrated distinct characteristics from nonsteroidal anti-inflammatory medications (8, 9). Research on the anti-cancer properties of frankincense and its derivatives has been shown significant promise against a variety of malignancies both *in vitro* and *in vivo* (10). Additionally, they are purported to have cancer-fighting properties as well (11).

Pentacyclic triterpenic acids exhibit various biological properties, like anti-inflammatory, anti-excitotoxic and antioxidative activities, which hold therapeutic potential for neurological disorders (12). BA exhibited antiproliferative properties in several types of cells. BA inhibited DNA topoisomerases I and II, consequently induced death in HL-60 cells (13). Additionally, BA may promote erythrocyte cell membrane phospholipid scrambling and cell shrinkage,

partially mediated by p38 protein kinase activity (14). In another study, the extract from *Boswellia serrata* displayed cytotoxicity in HepG2 and HCT 116 cell lines when compared with other classic drugs such as 5-fluorouracil and doxorubicin respectively (15). Moreover, the extracts from *B. serrata* dose-dependently induced HeLa cell death at concentrations of 0.5 - 2 mg/mL (16).

BA, such as 11-keto-β-boswellic acid (KBA) and acetyl-11-keto-beta-boswellic acid (AKBA) are selective, non-redox inhibitors of 5-LOX. Of the examined BA, AKBA was the most potent (IC50 = 1.5 - 50 µM), meaning that it required just 1.5 µM of dose to yield 50 % inhibition (9, 17, 18). AKBA triggered the caspase cascade (caspase-3, caspase-8 and caspase-9) in various tumor cell types, while simultaneously causing cleavage of PARP (poly ADP-ribose polymerase) and modulation of the PI3K/Akt pathway (phosphoinositide-3-kinase), leading to antiproliferative and apoptotic effects (19-21). Inhibiting the growth of tumors, metastasis and angiogenesis, AKBA can also encourage apoptosis. AKBA is also associated with the potential suppression of the NF-κB (nuclear factor κB) system , downregulation of the expression of COX-2, MMPs, CXCR4 (CXC chemokine receptor type 4) and VEGF (vascular endothelial growth factor) and the modulation of the EGFR (epidermal growth factor receptor), Wnt/β-catenin and ATM/P53 (ataxia-telangiectasia mutated) signaling pathways (22–25). Additionally, it has been discovered that AKBA binds and inhibits topoisomerases I and IIα (26).

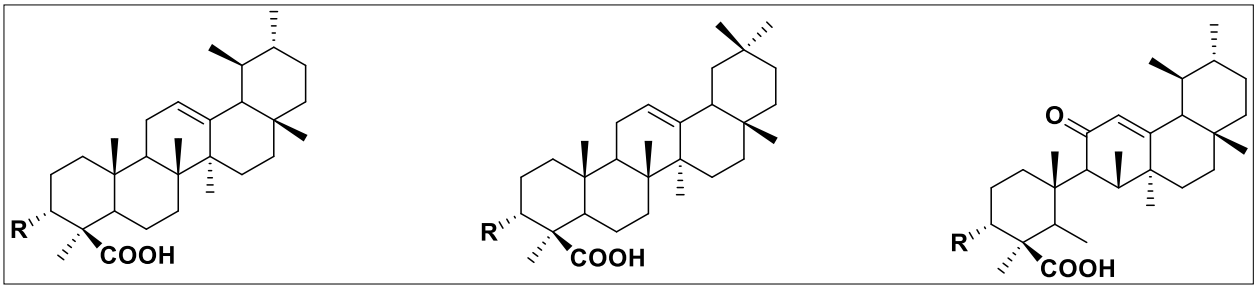
AKBA had the most potent anti-metastatic, anti-proliferative and apoptotic effects on various cancer cell lines *in vitro* (27). Nevertheless, 3-O-acetyl-β-boswellic acid exhibited the least harmful characteristics, as it did not induce apoptosis in MCF10A cells. Another positive aspect of 3 -O-acetyl-β-Boswellic acid for cancer chemoprevention is its ability to inhibit global DNA methylation in MDA-MB-231 and MCF-7 cells. It can be concluded from this review that 3-O-acetyl-β-Boswellic acid and AKBA, working together, may be an effective epigenetic operator and apoptotic factor for breast cancer, leading to less medication-resistant strains and more selective responses than traditional chemotherapies. The synergistic impact of 3-O-acetyl-β-Boswellic acid and AKBA should be further studied to achieve a promising medication for breast cancer therapy and also for other types of cancer. Also, this review summarizes the efficacy of BA in various types of cancer and provides a wide scope of study on the anti-cancer properties of BA in terms of development of novel drugs that would be more helpful both physically and economically. An electronic search was performed using Science Finder, Medline, Scopus and Google Scholar and collected English language articles from 2000 - 2025 relating to the role of BA in various types of cancer.

Composition of Frankincense

There is significant variability in the chemical composition of frankincense obtained from various *Boswellia* species. This means that composition is dependent on environmental and harvesting conditions, such as geographical location and seasons (7, 28). Frankincense consists of 55 – 75 % resins (terpenes mixtures), 25 - 30 % gums (polysaccharides mixtures) and 5 - 15 % essential oil (29, 30). In BA, the active functional group in the pentacyclic triterpenes makes up the resin component. But the gum part is made up of sugars like, pentose and hexose sugar, along with oxidizing and digestive enzymes. Monoterpenes, diterpenes and sesquiterpenes are all components of the essential oil (31). BA, the acidic component of olibanum, was initially described in a study and its chemical formula is $C_{32}H_{52}O_4$ (Table 1) (32). AKBA structures were first reported in an earlier study (33). By revealing the functional group's stereo-identity, the axial carboxyl and hydroxyl functions in BA, as well as assigning configurations at C-5, C-8, C-10, C-13 and C-17 was chemically proven (Fig. 1) (34). Physiochemical studies have revealed that

Table 1. Boswellic and lupeolic acids naturally found in *Boswellia* species

Name of the compound	Chemical formula of the compound	Molecular weight of the compound (g/mol)
β-BA	$C_{30}H_{48}O_3$	456.7
3-AKBA	$C_{32}H_{48}O_5$	512.7
α-BA	$C_{30}H_{48}O_3$	456.7
Lupeolic acid	$C_{30}H_{48}O_3$	456.7
11-Keto-β-boswellic acid	$C_{30}H_{46}O_4$	470.7
11-Hydroxy-β-boswellic acid	$C_{30}H_{48}O_4$	472.7
3-O-ABA	$C_{32}H_{50}O_4$	498.7
3-O-Acetyl-11-hydroxy-β-boswellic acid	$C_{32}H_{50}O_5$	514.7
11-KBA	$C_{30}H_{46}O_4$	470.7
3-O-Acetyl-9,11-dehydro-α-boswellic acid	$C_{32}H_{48}O_4$	496.7
3-ABA	$C_{32}H_{50}O_4$	498.7
11-Hydroxy-α-boswellic acid	$C_{30}H_{48}O_4$	472.7



(1) β-BA; R=OH (2)β-ABA; R=AcO | (1) α-BA; R=OH (2) α -ABA; R=AcO | (1) KBA; R=OH (2) AKBA; R=AcO

Fig. 1. Chemical structures of main BA.

Boswellia resin oil is composed of 42.5 % diterpenes, 13.1 % monoterpenes and 1 % sesquiterpenes. Other important constituents of the oil include o-methyl anisole (7.6 %), octyl acetate (13.4 %), alpha-pinene (3.1 %), thunbergol (4.1 %), decyl acetate (1.2 %), sclarene (2.9 %), verticiol (1.2 %), octyl formate (1.4 %), n-octanol (1.1 %) and 9-cis-retinal (2.8 %) (18, 35).

It has been reported that BA inhibited the HepG2 cell lines proliferation with a lower IC50 as compared to naringenin and curcumin dose-dependently. This promising anti-cancer potential of BA offers a future hope for the treatment and prevention of various cancers (36). It was also found that *P. harmala* and *B. serrata* extracts also exhibited a more potent cytotoxic effect at lower doses (37). Further *in vivo* studies are needed to identify the specific bioactive natural substances responsible for cytotoxicity in HeLa cells.

Olibanum in *Boswellia* species

In producing olibanum or Frankincense, 4 *Boswellia* species are well-known that are *B. serrata,* which is native to India; *Boswellia carterii,* which is indigenous to China and East Africa; *Boswellia frereana,* which is native to Somalia and Northeast Africa; and *B. sacra*, which is indigenous to the Middle East (Oman and Yemen) (18). Today, the production of frankincense predominantly occurs in Yemen, Somalia and Oman (3). Frankincense has a long history of medicinal values across the Middle East, India, Africa and China, most notably in treating and inhibiting chronic inflammatory disorders (2, 38). For centuries, Salai guggal, also known as Indian frankincense, has been employed due to its anti-proliferative, anti-arthritic, anti-inflammatory and analgesic properties in Indian traditional medicine (8). In traditional Chinese Medicine (TCM), the use of *B. carterii* has been reported for the treatment of enduring diseases such as leprosy and gonorrhoea, relieving cancer pain and enhancing the circulation of the blood (39). In an ever-expanding number of European countries, olibanum has been used for the purpose of treating various chronic inflammatory diseases, including peritumoral brain oedema, inflammatory bowel disease, arthritis and asthma (7).

Phytochemical investigation of the methanolic extracts of *B. serrata* has enabled the isolation and identification of β-Boswellic Acid. Innate triterpenoid boswellic acids such as this exhibit anti-carcinogenic and anti-tumor properties and display increased cytotoxic activity against the HCT 116 cell line (40). BA showed growth inhibition and induced apoptosis in colon cancer HT29 cells (39). Several studies have shown that BA activates the caspase-3 cascade and modulates the pro-apoptotic Bcl-2 family of proteins (death receptor-mediated apoptosis) as well as upregulates cell death receptors, including TNF-related apoptosis-inducing ligand death receptors (DR4) and TNF receptor-1 (TNF-R1) (41). In line with this, BA upregulated CATT/enhancer binding protein homologous protein expression and stimulated the expression of death receptor-5 in human prostate cancer LNCaP and PC-3 cells (20). Previously, it has been reported that *B. serrata* isolated volatile oils exhibit toxicity against the HCT 116 cell line. Essential oil isolated from *Boswellia* species displayed selective cytotoxicity and apoptosis in colon cancer cells when compared to normal cell lines (15, 42). For instance, *B. serrata* volatile oils exhibit anti-proliferative and pro-apoptotic properties, which, when combined, inhibit cell proliferation (43). Additionally, frankincense essential oils have the potential to reverse multiple drug resistance in human malignancy cell lines (20).

Following the synthesis and characterization of 11-keto-α-boswellic acid (αKBA), a novel triterpenoid using 1D and 2D NMR, in conjunction with HR-MS analysis, the researchers devised a reliable and sensitive HPLC-MS/MS method for identifying and measuring individual KBA (30). This facilitated the investigation of 41 different *Boswellia* oleogum resins, which revealed that 11-keto-β-boswellic acid (β-KBA) isomer α-KBA is an essential therapeutic constituent in *Boswellia* species. Notably, α-KBA displayed cytotoxicity against human breast cancer TNBC cell lines that are resistant to chemotherapy. The lipophilicity and cytotoxic effect of β-KBA is increased by acetylation of the β-isomer. However, additional research is required to determine the relationship between the chemical structure of BA and their biological activity to develop new anti-tumor medicines and our discoveries shed light on that relationship (30, 44).

Pharmacotherapeutic actions of Boswellic acids

Anticancer activity

Cancer is a complex group of diseases that adversely impact human lives, as both incidence and fatality rates are persistently increasing globally (45). Most of the treatments that are currently available have highly adverse effects on individuals because they have reached ineffectiveness due to chemo-resistance (46, 47). Consequently, researchers have shifted their focus to natural chemicals such as curcumin, emodin, butein, EGCG (epigallocatechin gallate), resveratrol, honokiol and celastrol for cancer treatment and prevention (48). Among phytochemicals, BA has the potential to prevent or effectively cure pancreatic, lung, liver, head and neck, colorectal, prostate, cervical, bladder and breast cancers (Fig. 2). Several researches (including both *in vivo* and *in vitro*) have shown the efficacy of BA in killing cancer cells (Fig. 3) (10).

However, the stress in the endoplasmic reticulum, generated by reactive oxygen species (ROS), must be modulated, as BA induces changes in transcription, epigenetic factors and signal transmission. Some of the alterations in gene expression caused by BA include an arrested cell cycle, inhibited growth, activation of apoptosis and regulation of inflammation (49).

Anti-tumor chemicals such as triterpenoids have been identified in the oleogum resins of several *Boswellia* species (50). Studies have revealed that 4 triterpenic acids extracted from *B. serrata* gum resin: BA, acetyl-β-boswellic acid (ABA), KBA and AKBA, suppressed oncogene expression as well as protein production in human leukemia HL-60 cells. Although the viability of cells remains unchanged, the proliferation of HL-60 cells is significantly reduced by AKBA (51). Among the 6 different types of human myeloid leukemia cells, Boswellic acid acetate appears to initiate cell death by activating a caspase-mediated mechanism involving death receptors 4 and 5 (DR4, DR5) (52). The anti-tumor properties of AKBA are

Fig. 2. Activity of BA in different types of cancer.

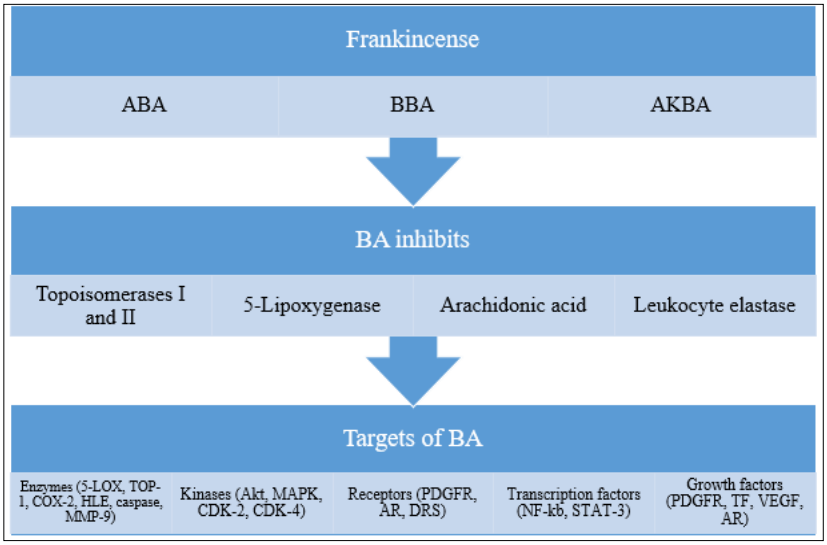


Fig. 3. Schematic diagram of the mechanism of BA against different types of cancers by inhibiting various enzymes, receptors and growth factors.

mediated by the inhibition of lipoxygenases, which reduces tumor cell proliferation and induces the death of cells (53).

Essential oil from *B. sacra* obtained by hydrodistillation displays tumor cell-specific cytotoxicity against different types of cancer cell lines (42). This was also confirmed in drug-resistant and metastasised breast cancer, affirming its anti-invasive, pro-apoptotic and antiproliferative activity in breast cancer cells. Their findings indicated that *B. sacra* essential oil inhibited the expression of cyclin D1 and cdk4 in breast cancer cell lines. Further research is needed for the biological basis of the relationship between the essential oil regulation of PI3K/Akt and ERK1/2 activation, cdk4 and cyclin D expression and tumor cell cytotoxicity.

Breast Cancer

For the management of breast cancer, an *in vitro* study was conducted involving MDA-MB-231 cells to investigate the potential activity for *B. serrata* extract (BSE) and 3-O-Acetyl-β-BA (3-OABA). BSE and 3-OABA proved effective in combating triple-negative breast cancer and played a role in regulating activated programmed cell death (APCD) by regulating phosphorylation of ERK and modulation of UPR, which supports cell proliferation and malignancies. Moreover, BSE and 3-OABA substantially modulated gene expression by regulating Tribbles homolog 3, mTOR inhibitors-sestrin 2, endoplasmic reticulum stress-inducible HERPUD1, glutathione-depleting ChaC, cystathionine gamma-lyase (CTH) and homocysteine-inducible expression levels (54).

BA eradicated the breast tumor by decreasing the expression level of CXCR4 protein (24). BA induced cell death by the significant reduction in anti-apoptotic protein B-cell lymphoma 2 protein (Bcl2) levels and an increase in pro-apoptotic protein Bcl-2-associated X (Bax) expression. BA also exerts synergistic effects in triple-negative breast cancer cells and increased cytotoxicity and sensitivity to cisplatin and doxorubicin (55). When BA was administered along with radiation therapy, it was well tolerated in radiation-treated pancreatic cancer patients, exhibiting reduced erythema and fewer cutaneous side effects (56). In human PC cell lines, BA increases cell death and reduces viability through activation of the caspase-dependent pathway, indicating that it has the potential to treat pancreatic adenocarcinoma (57). For both treating cancer and enhancing the chemotherapeutic response, potential molecular targets for BA are the extracellular signal-regulated kinase (ERK)1/2 and Akt strains, as BA may block both of these in human breast and PC cell

lines (58).

A comparative study identified 16 frankincense nutraceuticals (FN) that displayed significant variation in their chemical composition, cytokine modulatory capabilities and cytotoxicity against triple-negative breast cancer cells. For instance, FN that contained more than 30 % Boswellic and Lupeolic acids (BA and LA) in total and/or greater than 36 µg/mg of β-ABA essentially suppressed the proinflammatory cytokines TNF-α and IL-6. *In vitro* experiments with triple-negative breast cancer cell lines (MDA-MB-231, MDA-MB-453 and CAL-51) indicated that FN is cytotoxic, with the most efficacious FN containing levels of LA and BA above 30 % BA and levels of β-ABA levels above 50 µg/mg. The combination of one of these FN and pure β-ABA resulted in the inhibition of *in vivo* growth and triggered apoptosis in breast cancer xenografts. Furthermore, significant correlations were identified between cytokine inhibition, cytotoxicity and the contents of BA and LA in breast cancer cells. Against breast cancer cells, the highest association was found between α-ABA and β-ABA in the inhibition of TNF-α and IL-6, as well as the production of IL-8 cytokine and cytotoxicity. Additionally, the results of both in vitro and in vivo studies have demonstrated the effectiveness of pure β-ABA in destroying breast cancer cells. Thus, β-ABA must be regarded as a component in the standardization of frankincense nutraceuticals and herbal solutions and additional research should be conducted in this regard to develop novel anti-tumor medications (59).

In contrast to traditional chemotherapies, the incidence of multidrug resistance (MDR) and the potential for higher selectivity in breast cancer treatment can be achieved by combining epigenetic operator 3-OABA–with AKBA, an apoptotic factor (27). To create a favorable medication for breast cancer therapy, further investigation is required regarding the synergistic effect of 3-OABA and AKBA.

The prognosis of individuals who receive a diagnosis of triple-negative breast cancer (TNBC) is extremely poor. Chemotherapy remains the primary therapeutic option for TNBC as, unlike HER2+ and hormone receptor-positive breast cancer, TNBC fails to respond to targeted therapy; hence, treatment for this cancer is not yet efficient. Regulated by the insulin-like growth factor 1 (IGF-I) axis, vital signalling pathways in breast cancer development include MAPK, PI3K/AKt and JAK/STAT (60).

Brain Cancer

In 2012, 256213 people across the world (116605 females and 139608 men) were reported to have a primary malignant brain tumor (61). Constituting almost 50 % of all gliomas, glioblastoma constitutes the primary brain tumor that is the most prevalent, aggressive and fatal in adults. After being diagnosed, patients with GBM typically live for 15 - 20 months, with just 3 - 5 % of patients surviving for more than 5 years, even if treatment regimens are optimal (62, 63). According to a study it was found that if the cell cycle is arrested during the G2/M phase, AKBA human glioblastoma tumor growth can be inhibited, resulting in mitochondrial-dependent death (64). The essential phases in this process are regulation of the p21/FOXM1/cyclin B1 signalling pathway and mitosis suppression via downregulation of the Aurora B/TOP2A pathway. There is increasing evidence that AKBA could serve as an effective chemotherapeutic medication for glioblastoma patients. In a study, it was reported that BA displayed cytotoxicity against malignant glioma cells at reduced micromolar concentrations (65). Furthermore, exposure to pure extracts of *B. serrata* gum resin and other BA analogs like β-BA, AKBA and cyanoenone of methyl boswellates (CEMB) demonstrates that glioma cells are vulnerable to cytostatic and apoptosis-inducing effects (64, 66). In addition, suppression of the ERK signal transduction pathway could partially mediate the cytotoxic effect of AKBA in meningioma cells (22). Further, the anti-tumor effect of CEMB has been shown in experiments carried out on immunocompromised mice using a xenograft of C6 glioma tumors, revealing that tumor development can be substantially reduced by implementing CEMB as an intratumor treatment (67).

Studies involving patients diagnosed as having malignant glioma had shown that in 8 out of 12 patients, the administration of 3600 mg of *B. serrata* extract per day (containing 60 % boswellic acids) over 7 days before surgery caused the amount of fluid surrounding the tumor to reduce by 30 % on average. Moreover, during treatment, there was a noticeable decrease in signs of brain damage. A comprehensive study on patients with malignant brain tumors receiving *Boswellia* extract and undergoing radiotherapy revealed a 75 % reduction in cerebral edema comprehensive study on patients with malignant brain tumors receiving *Boswellia* extract and undergoing radiotherapy revealed a 75 % reduction in cerebral edema in 60 % of these patients upon completion of radiotherapy. In addition, the tumor-to-volume ratio also decreased, suggesting an anti-tumor effect (68).

According to a study, a patient suffering from gliosarcoma revealed that *B. sacra* might save steroids and exert a positive impact on the response of the tumor to radiotherapy as the size of the tumor had gradually been reduced (69).

Colon Cancer

BA has been known to be effective in averting colon cancer in multiple studies both *in vivo* and *in vitro*. Research on the apoptotic and anti-proliferative effects of BA has shown that it induces cell death in HT29 colon cancer cells through a caspase-8-dependent pathway and inhibits cell proliferation through a p21-dependent pathway (70, 71). Its efficacy against colon cancer cells also reduces the regulatory role of BA on β-catenin signaling molecules, which are important factors influencing the growth of cancer cells (58). Furthermore, when pre-incubated with BA, the death of HT-29 cells is dramatically improved by phosphatidylinositol 3-kinase (PI3K) inhibitors, including LY294002 or wortmannin (64). Additionally, AKBA suppressed intestinal adenomatous polyposis in the small intestine and colonic polyps by inhibiting Wnt/β-catenin and NF-κB/cyclooxygenase-2 (COX-2), which induces apoptosis in mice (72). Furthermore, immunohistochemical staining has revealed that expression of Ki-67 and CD31 in the orthotopic tumors of nude mice was significantly inhibited by AKBA treatment. A significant reduction in Ki-67 and CD31 are indicators of proliferation and differentiation for colorectal cancers linked to inhibition

of distant metastasis to the spleen, lungs or liver (73).

Another study examined the antiproliferative and apoptotic activities of β-BA, KBA and AKBA, all of which are analogues of BA. The results indicated that activation of caspases and the p21-dependent pathway are the principal mechanisms for AKBA-induced apoptosis (39, 74). Based on *in vitro* experiments involving human colon cancer cells, it was shown that apoptosis induction and cell cycle arrest, along with PI3K/Akt signalling pathway abrogation, mediate the powerful anti-tumor effects of BA (75). AKBA not only has an impact on genetic (CD31 and Ki-67) and epigenetic effects (demethylation and miRNA regulation), but also plays a key role in the proliferation of cells in colorectal cancer (76, 77). Moreover, through the modulation of specific cancer-associated microRNAs, such as miR-34a and miR-27a, in colorectal cancer cells, AKBA and curcumin demonstrate anti-tumorigenic activity both *in vivo* and *in vitro* (78).

An experiment conducted in which the anti-cancer properties of *B. serrata* methanolic extract on human colon cancer cells were investigated investigate the anti-cancer properties of *B. serrata* methanolic extract on human colon cancer cells (79). The results revealed that multiple genes and proteins involved in cyclooxygenase-2, such as mPGES-1, VEGF, CXCR4, MMP-2, MMP-9 and even hypoxia-inducible factor-1 (HIF-1), were reduced by the methanolic extract.

Leukaemia

Antileukemic activities of BA's and its derivatives (β-BA, KBA, AKBA) were assessed in leukemic cell lines MOLT-4, HL-60, K562, CCRF-CEM, THP-1, ML-1, U937 and NB4 SKNO-1 cells. The findings indicated that the cytotoxic and cytostatic effects of BA administration are attributed to the induction of apoptosis. Moreover, these molecular mechanisms also result in a progressive reduction of topoisomerases I and II, cytochrome c release, caspase activation, lowered mitochondrial membrane potential and PARP fragmentation due to the therapy. Researchers have concluded that the drug-reduced expressions of TNF-α and IL-1β, MMP-1 and MMP-2 and mRNA for MMP-9 inhibit ERK 1/2 and p38 MAPK phosphorylation and disrupt PI3K/AKT/Hsp90 cascade (13, 80)

Regarding *B. serrata*, studies have sought to determine the anti-cancer activities of 4 BAs (β-BA, KBA, 3-OABA and 3-OAKBA). In human leukemia cells known as HL-60 cells, they targeted leukemia cells, known as HL-60 cells; they target the restriction of DNA, RNA and protein synthesis. It was found that protein, DNA and RNA production was significantly impeded by 3-OAKBA. The effect of this compound on DNA synthesis is permanent and HL-60 cell development is inhibited without any loss of functionality. This research affirmed that this promising new agent could be effective in putting an end to human leukemia (44, 81).

Prostate Cancer

GLOBOCAN reported that approximately 1.1 million people globally were newly diagnosed with prostate cancer in 2012 (82–84). Studies have found that AKBA activates Caspase-3 and inhibits IκB kinase activity in the active NF-κB signalling pathway, leading to a reduction in the proliferation of cells and triggering apoptosis in PC-3 prostate cancer cell lines (46). Additionally, AKBA induced cell death by activating a death receptor 5-dependent cleavage of Caspase-3 and -8, as well as PARP, in prostate cancer LnCaP and PC-3 cells (20). There is compelling evidence that angiogenesis is mediated by VEGFR2 associated with prostate cancer metastasis. AKBA treatment inhibited angiogenesis by suppressing VEGFR2 (23). The proliferation of prostate cancer cells resistant to docetaxel is slowed as a result of blocking the STAT3 and Akt signalling pathways (85).

The results of *in vitro* and *in vivo* works have revealed that chemotherapy-resistant androgen-independent prostate cancer cells are restricted from growing by AKBA. Furthermore, BA causes the synthesis of NF-B-dependent anti-apoptotic proteins like as Bcl-2 and cyclin D1 to be decreased by inhibiting the constitutively active NF-kB pathway (86). In human PC-3 prostate cancer cells, the capacity of AKBA to activate caspase-3 is partly responsible for apoptosis, which has become resistant to chemotherapy. In LNCaP prostate cancer cells, cell death is initiated by AKBA via a mechanism controlled by death receptor 5. Caspase-3 and caspase-8 are activated when AKBA is used and they begin to cleave PARP (20). Furthermore, AKBA limits the expression of the androgen receptor, delaying the cell cycle process during the G1 phase and reducing cyclin D1, thereby inhibiting cell proliferation (87).

In prostate cancer, AKBA is capable of inhibiting angiogenesis mediated by vascular endothelial growth factor receptor 2 (5). In addition, tirucallic acids extracted from *B. carterii's* oleogum resin are potent Akt inhibitors their cytotoxic effects on human prostate cancer cell lines have been observed both *in vitro* and *in vivo* (50).

Liver Cancer

Liver cancer or hepatocellular cancer was the cause of approximately 745500 cancer-related deaths in 2012, with 782500 new cases documented (88–91). Studies evaluating the effects of KBA and AKBA revealed that they cause inhibition in the proliferation of cancer cells and finally induce death in liver cancer cells through the caspase-8-dependent pathway (19). A growth-modulatory and apoptogenic effect is exhibited by BSE in hepatocellular carcinoma cells, both alone and in combination with DOX, resulting in elevated TNF-α and IL-6 levels, as well as increased caspase-3 activity (90). Novel experiments demonstrated that AKBA induced senescence through the damage response of DNA and the inhibition of genes involved in repairing such damage – a unique mechanism designed to reduce HCC cell proliferation (92). Recent research has demonstrated that the anti-HCC effects of myrrh and frankincense are mediated by the MAPK and PI3K/Akt pathways, suggesting that these BA compounds may have potential for future HCC treatment (93).

Pancreatic Cancer

Globally, pancreatic cancer is ranked as the 7th leading cause of death among all cancers, with levels of incidence and mortality cases rising at similarly high rates (94). The bio function of AKBA has been assessed in both pancreatic cancer cell lines (13AsPC-1 and PANC-28) and animal models. Prior research has revealed that AKBA can inhibit the

proliferation of cancer cells and the expression of specific proteins in tumor tissues. The results indicated that AKBA significantly inhibits the growth of 4 lines of pancreatic cancer cells: 2 carrying p53 and K-Ras mutations (AsPC-1, one p53 mutant and BxPC-3, which has a wild-type K-Ras) and a third line that is mutant for p53 but not K-Ras (PANC-28) (24). A study recently reported that BA nanoparticles and diabetes medicine metformin synergistically promote the pro-apoptotic suppression of pancreatic cancer growth (73). By targeting numerous sites and inhibiting metastasis in a mouse model, BA was found to have suppressed the development of human pancreatic tumors (95).

Melanoma

Melanoma poses significant risks on a global scale, particularly for individuals with a fair complexion (96). In an *in vitro* study, the behaviour of the isomeric molecule, BC-4, comprising both α and β-BA acetate, was evaluated. At a concentration of 25 μM for 48 hr, BC-4, in conjunction with B16F10 cell differentiation and G1 arrest in the cell cycle, increases the migratory capacity of B16F10 cells and decreases topoisomerase II activity. Moreover, when fibrosarcoma cells are treated with this compound, BA increases HT-1080 apoptosis and decreases MMP secretion (39).

As reported in a study, in B16-F10 and FM94 but not HNEM (human epidermal melanocytes) cells, *in vitro* anti-melanoma activity of the FEO is demonstrated by causing death through caspase signalling of an MCL-1 dependent pathway (97). In addition, FEO was found to have decreased tumor size in a melanoma tumor model using C57BL/6 mice. Thus, as well as enhancing hematological biochemical markers, liver histology and phase I and phase II drug metabolizing enzymes, FEO may become the most effective medicine with respect to preventing hepatic injury.

Colorectal cancer

The complex nature of colorectal cancer is attributable to mutations in numerous oncogenes and tumor suppressor genes and also epigenetic modifications (98). AKBA is capable of targeting key oncogenic proteins, including nuclear factor kappa B and 5-lipoxygenase and exhibits chemo-preventive properties. Due to their of chemopreventive activity and several BA is known to regulate specific miRNA pathways. Notably, let-7 and miR-200 are among the potential tumour-suppressing microRNAs in the paths. AKBA promotes a significant increase in the expression of these families in multiple colorectal cancer cell lines. Research has reduced miRNA levels can suppress let-7shown that let-7 can be suppressed by reduced miRNA levels, leading to the stimulation of widespread migration and invasion of cancer cells. AKBA has been found to regulate a spectrum of miR-200 and let-7 downstream targets, including vimentin, CDK6 and E-cadherin. Expression of these downstream genes was also strongly regulated in nude animals transplanted orthotopically with CRC cells. This finding aligns with previous studies that have established the growing paradigm that BA can modulate epigenetic pathways in cells. This provides further evidence of their anti-tumor activity and their potential for use in preventing and treating CRC (77).

Lung Cancer

An *in vitro* investigation using H446 cells revealed the anti-tumor activity of 11-carbonyl β-Boswellic acid. The results indicated that its inhibitory effects on lung cancer cells are attributed to the JNK signalling pathway being activated, poly ADP-ribose polymerase (PARP) cleavage and downregulation of surviving protein expression (99). Another study reported cleavage of PARP on HOP-62 lung cancer cells following treatment with 3-α-propionyloxy-β-boswellic acid (POBA). As a result of the therapy, the cell cycle was arrested and apoptosis was induced (100). Recent research found that AKBA has the potential to increase its membrane fluidity and, indirectly, induce lung carcinogenesis by benzo(a)pyrene lipid content (101). In addition, by altering the cell cycle distribution, inducing apoptosis and inhibiting autophagy by a p21-mediated pathway, non-small lung cancer cells become more sensitive to cisplatin (102). Additional studies have also shown that through regulation of the maspin-dependent AKT/FOXO1/p21 signalling pathway, AKBA promotes lung cancer cell radiotherapy resistance (103).

Bladder Cancer

Bladder cancer impacts almost 430000 people each year worldwide and is responsible for 165000 deaths (104). The principal risk factor for the urothelial subtype, which comprises 90 % of all bladder cancer cases, is smoking tobacco. Indeed, smoking is the cause of two-thirds of all bladder cancer cases, which doubles or even triples the risk of developing bladder cancer (105). An *in vitro* study investigated the anti-cancer effects of frankincense oil, the primary constituent of which is BA, on UROtsa cells (immortalised normal bladder urothelial cells) and J82 (human bladder cancer). The results revealed that frankincense oil treatment is cytotoxic to J82 cells but does not affect UROtsa cells. This indicates that frankincense oil reduces the viability of tumor cells and can distinguish normal from malignant cells (43).

Cervical Cancer

Cervical cancer is responsible for the deaths of 265700 women each year and is ranked as one of the most prevalent cancers in females globally (106). DNA fragmentation, cell cycle arrest and mitochondrial membrane potential loss in SiHa cells are induced by the PARP cleavage that took place following POBA therapy in cervical cancer cells (100). Another study reported the use of oral contraceptive (OC) pills as being an independent risk factor for cervical cancer development (107) (Table 2) (Fig. 4).

Therapeutic potential of boswellic acids

BA exhibits apoptotic and antiproliferative effects on specific cancer cells, which could have clinical implications. Thus, clinical trials, animal models and *in vitro* studies have been conducted to investigate the anti-inflammatory properties of BA. The connection between chronic inflammation and cancer is well established. According to the medical literature, BA can lessen peritumoral oedema and potentially be employed for the alleviation of inflammatory disorders such as rheumatoid arthritis (RA), asthma, osteoarthritis (OA) and inflammatory bowel disease (IBD). When applied in the clinic via an oral or topical route for inflammatory bowel disease (IBD), ulcerative colitis and bronchial asthma, BA is tolerable. The aforementioned acids are reasonably non-

Table 2. Targets and mechanism of action involved in different types of cancers

Cancer Type	Targets	Mechanism	Reference
Breast cancer	Cyclin D1 and cdk4	Upregulation	45
Brain cancer	Aurora B/Top2A C6 glioma tumors	Mitosis suppression by downregulation Intratumor treatment	67,70
Colon cancer	HT29 cells	P21-dependent pathway	73
Leukemia	HL-60, K562, MOLT-4, THP-1, CCRF-CEM, ML-1, NB4, SKNO-1 and U937 cells	Attenuation of topoisomerases I and II, PI3K/AKT/Hsp-90 cascade	13, 83
Liver cancer	HCC cells	MAPK and P13K/Akt signaling pathways	96
Prostate cancer	PC-3 cells docetaxel-resistant prostate cancer cells	NF-κB signaling pathway STAT3 and Akt signaling pathway	46, 88
Pancreatic cancer	AsPC-1 and PANC-28 PC cell lines	Downregulation Caspase-dependent pathway	22, 60
Melanoma	B16F10 cells	Upregulation	41
Colorectal cancer	Ki-67 and CD31	P21-dependent pathway	76
Lung cancer	H446 cells HOP-62 cells LC cell	JNK signaling pathway PARP cleavage AKT/FOXO1/p21	102, 103, 106
Bladder cancer	J82 cells	Nrf2-mediated oxidative stress pathway	46
Cervical cancer	SiHa cells	PARP cleavage	103

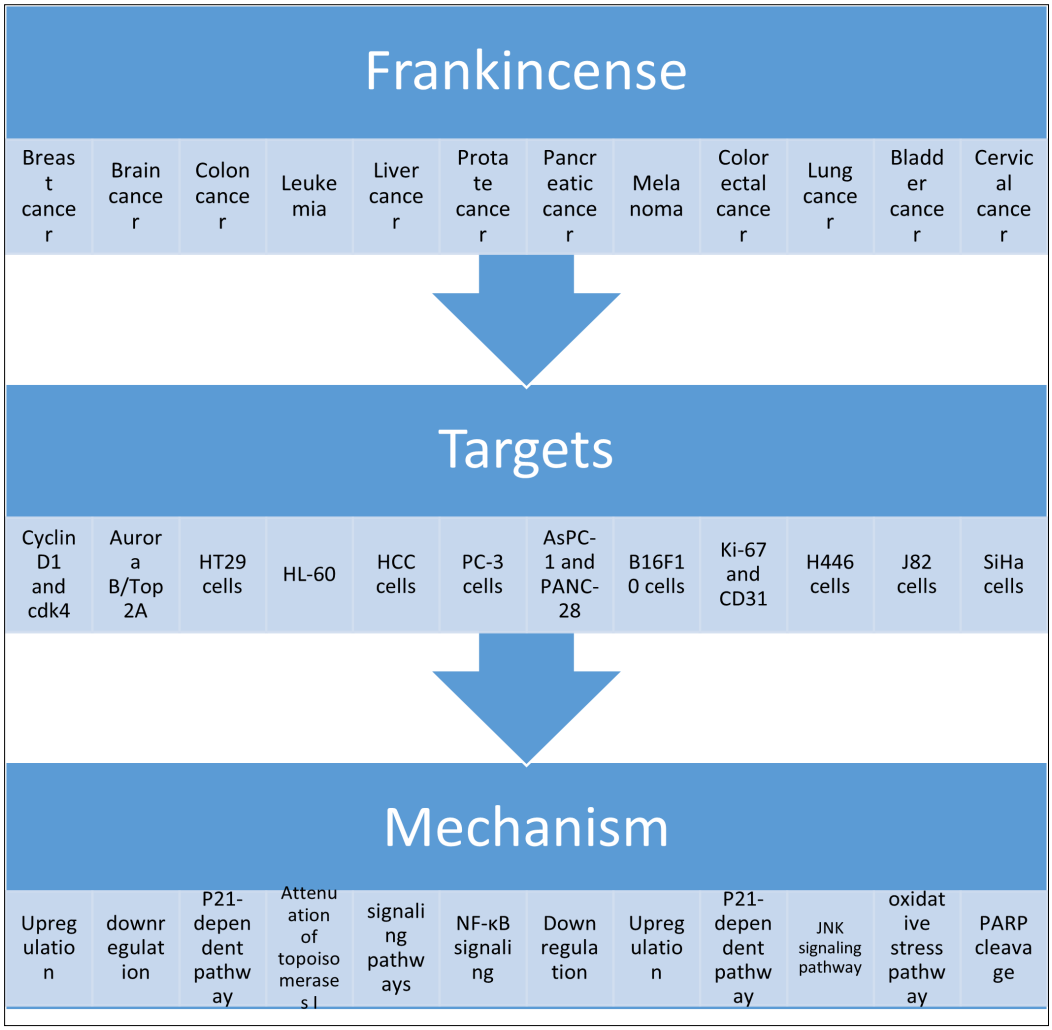


Fig. 4. Schematic diagram of the mechanism of Frankincense against different types of cancers by inhibiting specific targets and specific mechanisms.

toxic, which means a hefty dose of 500 mg/kg per day can be given orally or administered intrarectally.

AKBA exhibits high therapeutic potential as an anti-tumor agent. Research has revealed that it can inhibit multiple VEGFR2-related processes, including angiogenesis, cellular proliferation and survival, as well as osteoclastogenesis and apoptosis (both cytostatic and cytotoxic). Furthermore, its anti-tumor activity may be enhanced by the modulation of CXCR4. Specifically, AKBA inhibits tumor cell invasion by reducing the expression of CXCR4, a vital receptor in the interactions between tumor cells and their surroundings. The anti-tumor effects of AKBA in different cancers can be partly attributed to demethylation and the simultaneous activation of a subset of tumor suppressor genes. Most notably, research indicates that AKBA significantly attenuates tumor growth and angiogenesis via the mTOR and VEGFR2 signaling pathways, suggesting it may

have a valuable role to play in the treatment of various cancers (39).

Conclusion

In traditional and modern natural medicine, frankincense has historical and documented use for a variety of conditions with few side effects. This anti-arthritic, pain-relieving, anti-inflammatory and antimicrobial gum resin has been reported to have antiproliferative effects that can facilitate the alleviation of inflammatory pain, including, but not limited to, arthritis-related conditions. Interestingly, frankincense has the exceptional ability to induce dendritic segments and branching in hippocampal neuron cells, resulting in increased synapses and improved learning and memory. BA are being considered as prospective candidates for new medicinal products due to the increasing research work related to them. Among these, the most bioactive and representative BA is AKBA; thus, AKBA has been identified as a major candidate for assessing frankincense quality in applications for inflammatory-burdened disorders. The BA are valuable candidates as anticancer agents in general. Future studies on the compounds include the development of BA-based anticancer compounds, production-wise scale-up control devices, preparation of semisynthetic derivatives of pediatric BA and its analog and evaluation for its derivable mechanism on more potent BA derivatives.

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Authors' contributions

FK conceptualized and drafted the manuscript. LR contributed to the supervision of the review article and data analysis. LR and AS provided expertise and critical manuscript review. The manuscript was revised and finalized by FK. AS and AF provided valuable insights. All authors have read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: The authors declare no potential conflict of interest.

Ethical issues: The authors are responsible for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are thoroughly investigated and resolved.

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