Herbalism

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Review

Extraction of biologically active compounds by hydrodistillation of *Boswellia* species gum resins for anti-cancer therapy

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Abstract

Introduction

Essential oils produced by distillation processes from herbs and plants are traditionally confined to aromatherapy due to the abundance of low-molecular-weight, highly volatile, aromatic compounds. Essential oils are considered to be an alternative treatment that provides supportive care to cancer patients. Similar to the extraction process that involves the use of chemical solvents, essential oils produced from distillation procedures contain high-molecular-weight and biologically active compounds from plant materials. The aim of this review is to determine whether the use of biologically active compounds extracted from the *Boswellia* species gum resins is beneficial in anti-cancer therapy.

Conclusion

We have demonstrated that frankincense essential oils prepared by hydrodistillation of gum resins from *Boswellia* species contain complex chemical constituents and possess anti-cancer activity. Frankincense essential oil activates arrays of genes and pathways that suppress the growth and induce the apoptosis of established human cancer cell lines of different tissue origins. Besides boswellic acids, frankincense essential oil-induced anti-proliferative and pro-apoptotic activities in tumour cells may result from high-molecular-weight compound(s). Harvesting methods, storage conditions and geographic locations can alter the chemotypes of the natural product; therefore, good agriculture practices need to be implemented. In addition, standardisation of distillation procedures and identification of signature compound(s) will be required for quality assurance purposes. Results from preliminary clinical observations suggest that frankincense essential oil may be a viable therapeutic agent for treating a variety of cancers.

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Introduction

Aromatic gum resins obtained from trees of the genus *Boswellia* (family Burseraceae), also known as frankincense, have long been used in Ayurvedic and traditional Chinese medicines to treat a variety of health problems. In addition to their anti-inflammatory activity, frankincense extracts have been shown to suppress tumour development and induce tumour apoptosis in animal models[1,2]. In a human clinical study, a gum resin extract prepared from *Boswellia serrata* was found to reduce cerebral oedema with anti-cancer activity in patients irradiated for brain tumours[3]. Boswellic acids have been emphasised as the major component responsible for frankincense extract-mediated anti-tumour activity. Purified boswellic acids, particularly acetyl-11-keto-β-boswellic acid (AKBA), exhibit potent cytotoxic activities against cultured human neuroblastoma cell lines[4], meningioma cells[5], leukaemia cells[6], hepatoma cells[7], melanoma cells, fibrosarcoma cells[8], colon cancer cells[9], prostate cancer cells[10] and pancreatic cancer cells[11] in both *in vitro* and *in vivo* models. These studies demonstrate that gum resins of *Boswellia* species contain active ingredients that have potent anti-cancer activity.

Essential oils are extracted by distillation. In addition to classical uses of essential oils in aromatherapy, we have studied the anti-tumour activities of frankincense essential oil extracted by hydrodistillation of gum resins from *Boswellia* species. We have demonstrated that frankincense essential oil is highly effective in suppressing the proliferation and inducing the cytotoxicity of various human cancer cell lines in cultures and in an animal model[12–14]; however, such anti-cancer effects cannot be entirely attributed to boswellic acids. This review is based on the extraction of biologically active compounds from gum resins of the *Boswellia species* for anti-cancer therapy.

Discussion

The authors have referenced some of their own studies in this review. The protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. Animal care was in accordance with the institution guidelines.

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Figure 1: Harvest and grading of *B. sacra* gum resins. (a) Frankincense tree incision and tears. (b) Hougari Royal (or Najdi) grade resin harvested from desert area to the north of Dhofar State, Oman, northern to monsoon (rainy) area with very little rains. (c) Hougari Superior grade, with a green clear tinge, commonly placed in water by local people to relieve respiratory problems. (d) Hougari Regular grade, the common frankincense gum resin, is used for incense. (e) Hougari Sha'bi grade (the lowest) is harvested from old and dying trees in the coastal areas and areas within the monsoon.

Boswellia sacra gum resins and hydrodistillation

Frankincense resins are harvested from deep incisions made into the tree trunk of *Boswellia* species. This wounding process causes the tree to 'bleed' a milky white substance that seals and heals the wound to prevent infection (Figure 1a). To certify the harvest location, species and classification (Figure 1b–e), *B. sacra* gum resins were obtained directly from local collectors in the Dhofar Mountain region surrounding Salalah, Sultanate of Oman. To prepare frankincense essential oil, the *B. sacra* gum resin was processed in a custom-made hydrodistiller in Salalah, Oman[14]. The typical yield of frankincense essential oil by hydrodistillation is 10% (w/w) of gum resins within a range of 8%–13%.

Chemical components

Chemical composition and optical rotation of frankincense essential oils from *Boswellia* species are determined using chiral gas chromatography–mass spectrometry (GC–MS) and polarimetry, respectively. Chemical constituents of frankincense essential oils depend on geographical locations of trees, transportation, storage and processing procedures. We have distinguished the chemical properties ($P < 0.0001$) of the essential oils hydrodistilled from the gum resins of *B. sacra* and *Boswellia carterii*[15]. *B. sacra* essential oil possesses a positive optical rotation of polarised light (+30.1° with standard deviation of 5.4° for $n = 88$), while *B. carterii* essential oil is characterised with a negative optical rotation (−13.3° with standard deviation of 4.9° for $n = 39$). In addition, chiral GC–MS of the monoterpenes (especially the most abundant α-pinene: 79.0% in *B. sacra* and 48.2% in *B. carterii*) with a chiral centre demonstrated the reason for the differing optical rotations. The enantiomeric ratio of the (+)/(−) enantiomers of α-pinene was 8.24 for *B. sacra* essential oil versus 0.68 for *B. carterii* essential oil. Four other chiral monoterpenes had a greater abundance of the (+) enantiomer in *B. sacra* essential oil with (+)/(−) enantiomeric ratios ranging from 2.77 to 7.00, whereas the (−) enantiomer was more abundant in *B. carterii* essential oil with (+)/(−) enantiomeric ratios ranging from 0.04 to 0.85.

We have found that a quick measurement of the optical rotation by polarimetry can provide additional evidence of the local geographic source of the gum resins. For instance, *B. sacra* resins harvested from trees in the westerly Mughsayl area of the Dhofar Mountains yield essential oil distinctive of the easterly Hasik area gum resins. Mughsayl frankincense essential oil has a significantly higher percentage ($P < 0.0001$) of α-pinene

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Table 1. Temperature- and duration-dependent chemical composition of frankincense essential oils extracted by distillation.

Library/ID	Area (%)			
	78 °C 0–2 h	78 °C 9–10 h	78 °C 0–12 h	100 °C 12 h
trans-β-Caryophyllene	0.02	0.02	0.28	0.62
α-Humulene	0.03	0.01	0.11	0.17
Allo-aromadendrene			0.02	0.06
γ-Muurolene		0.01	0.05	0.10
Germacrene D			0.02	0.09
β-Selinene	0.01	0.02	0.21	0.45
α-Selinene	0.02	0.01	0.12	0.24
γ-Cadinene			0.04	0.07
δ-Cadinene		0.01	0.05	0.14
Caryophyllene oxide			0.02	0.05

(79.0% vs. 48.2%) noted by a similarly higher optical rotation of +30.2° versus +19.3°. Conversely, Hasik area frankincense essential oil contains higher quantities of myrcene (11.4% vs. 1.1%) and limonene (13.6% vs. 3.7%). The higher limonene content of Hasik area gum resins provides a 'sweet, orange' aroma that makes it more valuable to resin-burning consumers. These results have been confirmed by a recent report that α-pinene is the principal component and chemotaxonomical marker to identify the botanical and geographic source of *B. sacra* resins within the Dhofar Mountain range of Oman[16].

Hydrodistillation procedures determine the chemical constituents of the frankincense essential oil. For example, the abundance of high-molecular-weight compounds is positively associated with distillation time and temperature. Longer duration and higher temperature distillations produce greater amounts of high-molecular-weight compounds, such as sesquiterpenes and boswellic acids[13]. Table 1 schematically illustrates time- and temperature-dependent chemical compositions in frankincense essential oils. Based on GC–MS profiling, frankincense essential oil obtained at 100 °C for 24 h consists of more than 300 different identifiable compounds ranging in mass from 72 to 468 amu[14].

Molecular mechanism of frankincense essential oil-induced cancer cell apoptosis

We have demonstrated that frankincense essential oils prepared from hydrodistillation of *B. carterii* and *B. sacra* gum resins at 100 °C for 24 h possess potent growth suppression activity in cultured human bladder, breast, colon and pancreatic cancer cells. The growth-suppressing activity of frankincense essential oils results from a combination of anti-proliferative and pro-apoptotic activities[12]. In addition, frankincense essential oil overcomes multicellular resistance and suppresses invasive phenotypes of human cancer cells[14]. More importantly, human tumour cell lines are more sensitive to frankincense essential oil-induced growth arrest and apoptosis as compared with their normal counterparts, and similar results have been observed in cell lines derived from the bladder[12], breast[14] and colon. This is an important and unique characteristic of frankincense essential oil as compared with other essential oils, including lavender, sandalwood and others.

Consistent with results from cell viability assays, several gene products identified as frankincense essential oil-responsive genes are associated with suppression of cell proliferation and arrest of cell cycle progression. Frankincense essential oil up-regulates the expression of anti-proliferative genes, including *IL8*, *CLK1*, *DLG1*, *KLF4*, *NEDD9*, *CDKN1A*, *IL1A*, *IL6*, *SNFILK*, *SSTR1*, *IL1A* and *IL6*, as well as cell cycle arrest genes, including *DDIT3*, *IL8* and *CDKNIA* in human bladder cancer cells[12]. We have also demonstrated that frankincense essential oil suppresses the expression of cyclin D1 and cdk4 proteins in human cancer cell lines[13,14], and may result in blocking G1/S transition in cell cycle progression in these cells[17,18].

Frankincense essential oil also up-regulates a number of genes that are responsible for apoptosis, which include *CDKN1A*, *DEDD2*, *IER3*, *IL6*, *SGK*, *TNFAIP3*, *GAD45B*, *NUDT2* and others in human bladder cancer cells[12]. In addition, expression of a cell survival gene *AXL* is suppressed by frankincense essential oil. Consistent with results from boswellic acid-treated HT29 and HepG2 cells[7,19], frankincense essential oil-induced apoptosis is caspase-dependent based on the cleavages and activation of caspase-3, caspase-8, caspase-9, and poly(ADP-ribose) polymerase in various human cancer cell lines[13,14].

Frankincense essential oil activates multiple signalling pathways

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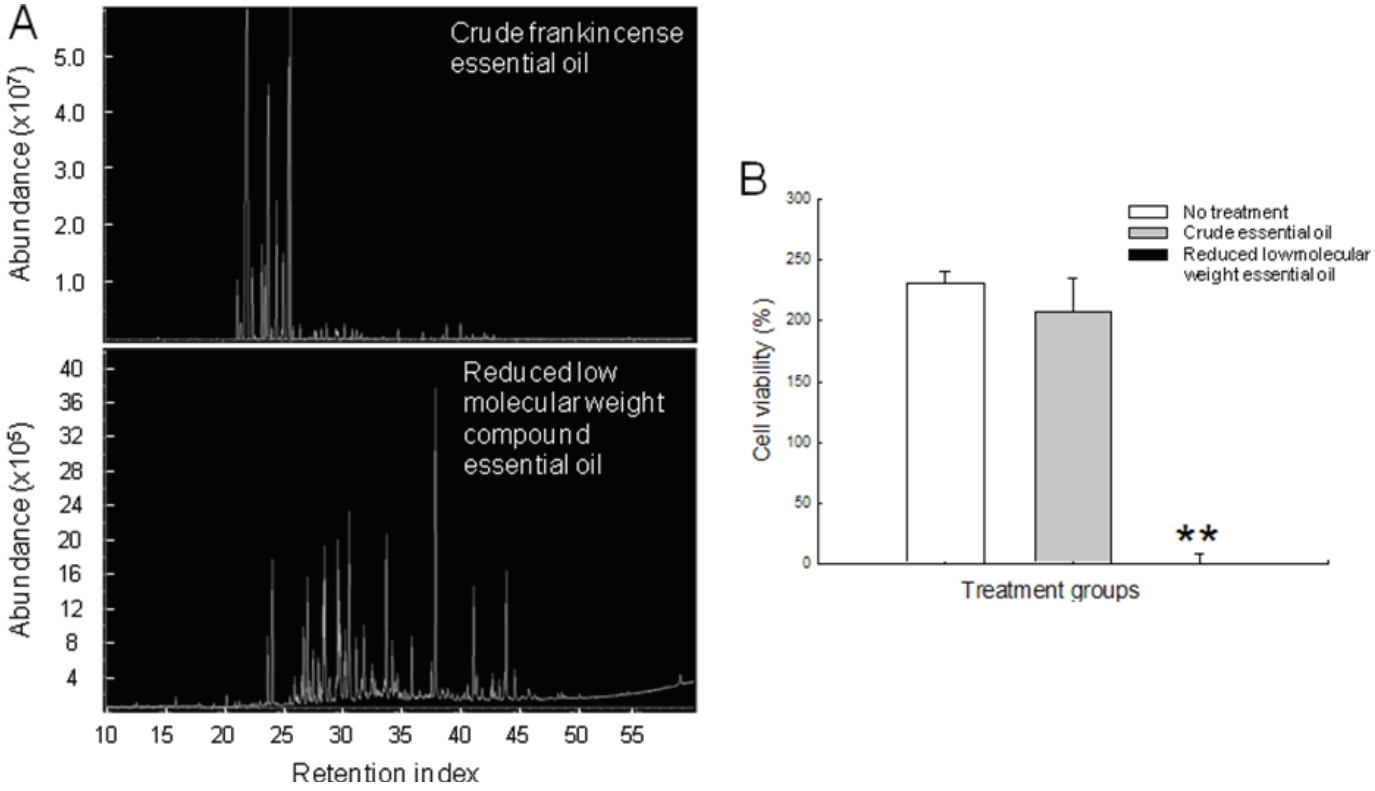

Figure 2: A correlation between chemical profile and tumour cell cytotoxicity of frankincense essential oils. (a) GC–MS profiles of crude frankincense essential oil after hydrodistillation and after differential fractionation. (b) Comparison between crude frankincense essential oil and essential oil with reduced low-molecular-weight compounds. Human pancreatic cancer MIA PaCa-2 cells were treated with the same concentration of crude and differentially fractionated essential oils in separate wells; and cell viability was determined by the XTT assay at 24 h after treatment. Double asterisks (**) indicate $P < 0.01$.

in cultured human cancer cell lines. We have shown that frankincense essential oil increases the levels of Akt phosphorylation at Ser(473) and enhances Erk1/2 activation in human breast and pancreatic cancer cells[13,14]. These results are consistent with reports that boswellic acids and AKBA activate the PI3K/Akt pathway in colon cancer HT29, HCT-116, SW480 and LS174T cells[20] and Erk1/2 in human polymorphonuclear leukocytes and platelets[21]. Activations of Akt and Erk1/2 pathways in cancer cells by anti-cancer compounds with pro-apoptotic activity have also been reported[22,23]. Significances of frankincense essential oil-modulated PI3K/Akt and Erk1/2 pathway activation in inducing tumour cell growth arrest and apoptosis require further studies.

Frankincense essential oil-modulated anti-tumour activity is also observed *in vivo*. Subcutaneous administration of frankincense essential oil significantly suppresses tumour growth and progression in a heterotopic xenograft human pancreatic cancer mouse model[13]. In agreement with frankincense essential oil-induced anti-proliferative and pro-apoptotic activities in cultured cancer cells, administration of frankincense essential oil suppresses the number of phospho-histone H3 (Ser10)-positive proliferative cells, and increases the number of terminal deoxynucleotidyl transferase dUTP nick-end labelling-positive apoptotic tumour cells as compared with the control group.

Identification of possible anti-cancer components in frankincense essential oil

Frankincense essential oil obtained from hydrodistillation of *B. sacra* gum resins has been studied to analyse the relationship between chemical composition and anti-cancer activity. We have reported that the abundance of high-molecular-weight compounds is positively correlated with frankincense essential oil-induced cytotoxicity in cultured human cancer cell lines. For example, frankincense essential oil prepared from distillation at higher temperature contains higher amounts of heavy molecular weight compounds and possesses more potent anti-cancer activity[13]. In addition, differential fractionations of frankincense essential oil produce reduced levels of low-molecular-weight compounds, and are significantly more potent than unfractionated essential oil in suppressing tumour cell viability (Figure 2). These results suggest that high-molecular-weight compounds

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and/or ratios of these compounds play important roles in frankincense essential oil-mediated anti-tumour activity.

Although boswellic acids, especially AKBA, have been enriched or purified from *Boswellia* species gum resins for studying their anti-cancer property, our results suggest that compounds other than boswellic acids might be equally or more important in frankincense essential oil-modulated anti-cancer activity. For example, contents of boswellic acids in frankincense essential oils are not proportionally related to essential oil-induced tumour cell death[14]. We also observed that frankincense essential oil enriched with high-molecular-weight compounds but with lower boswellic acid contents is significantly more potent in suppressing the viability of cultured human cancer cells. Additionally, frankincense hydrosol, the aqueous distillate of hydrodistilled *Boswellia* species gum resins, contains up to 15.5% boswellic acids, but did not have detectable cytotoxicity against tumour cells. Another compound, tirucallic acid, purified from *B. carterii* gum resins, has been found to induce human prostate cancer cell death[24]. With a complex chemical constituent in frankincense essential oil, many components may work synergistically to provide a potent anti-cancer activity. Although it might not be easy to isolate a group of compounds working synergistically, it is important to identify a signature compound(s) that assures consistent biological and anti-cancer activities.

Essential oils for cancer patients have been primarily emphasised as a supportive care for general well-being. Uses of essential oils are generally limited to inhalation or topical application in the United Kingdom and the United States; however, essential oils can be administered orally or internally in France and Germany. Since distillation process is intended to extract biologically active compounds from plant materials without the aid of chemical solvents, essential oils shall contain chemical constituents similar to those extracted from chemical solvents but with higher portions of low-molecular-weight compounds. Thus, essential oils shall be suitable for ingestion as long as signature compounds can be defined, and safety profiles can be established.

Based on a recent report, topical applications of frankincense essential oil distilled from *B. carterii* gum resins have been shown to be effective in the treatment of malignant melanoma in horses[25]. A similar approach can be applied to patients with bladder cancer, if appropriate doses of frankincense essential oil can be administered into the bladder through instillation.

Frankincense gum resins are used as a component in anti-cancer drugs in traditional Chinese medicine. A chemical extract of *B. serrata* gum resins has been investigated as an anti-cancer agent in patients irradiated for brain tumours, with no severe adverse effects being observed[3]. In an ongoing phase II clinical trial, a chemical extract of *Boswellia* species gum resins is studied as an adjuvant agent in patients with high-grade gliomas[26]. Frankincense essential oil obtained from them *B. sacra* gum resins has been further fractionated and administered to patients suffering from various types and stages of cancers in Arabic nations for oral ingestion. The fractionated frankincense essential oils have lower levels of low-molecular-weight compounds (proprietary information), and have been shown to have reduced adverse symptoms, including light-headedness, irritated stomach or diarrhoea. Patients responded positively after receiving a defined volume with specific chemical components of frankincense essential oil for a specific period of period (data not shown).

To prepare frankincense essential oil for anti-cancer therapy, standardised procedures to harvest, store and process *Boswellia* species gum resins have to be established to obtain consistent results. In addition, before the active ingredient(s) in frankincense essential oil is identified, standardisation of the product using GC–MS and high-performance liquid chromatography is our best approach to assure quality and efficacy. Although no serious safety and toxicity issues have been raised in animal models and patients receiving oral administration of frankincense extracts[27–31], the safe dose of essential oil needs to be defined for cancer therapy, and pharmacokinetics and pharmacodynamic properties of the essential oil need to be determined. Course to cancer recovery using frankincense essential oil may be very different from our current understanding of tumour regression using chemotherapy, radiation therapy or targeted therapy. The frankincense essential oil may activate the hosts' inflammatory responses to suppress tumour progression by its anti-inflammatory activity. Thus, additional clinical studies are required to understand the mechanism of frankincense essential oil-suppressed tumour progression in human subjects.

Conclusion

Frankincense essential oil obtained from the hydrodistillation of *Boswellia* species gum resins possesses anti-cancer properties by activating multiple signalling pathways, cell cycle regulators and caspase-dependent apoptosis. Safety and efficacy, pharmacokinetics and pharmacodynamics, as well as tumour and patient responses of systemic frankincense essential oil administration need to be studied. Frankincense essential oil can be a novel and alternative therapeutic agent to suppress cancer progression and metastasis with minimal adverse effects when an appropriate dose is defined.

Competing interests

CL Woolley and DG Young are affiliated with Young Living Essential Oils.

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The rest of authors declare that they have no competing interests.

Abbreviations list

AKBA, acetyl-11-keto-β-boswellic acid; GC, gas chromatography; MS, mass spectrometry.

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