



Frankincense (乳香 Rǔ Xiāng; *Boswellia* Species): From the Selection of Traditional Applications to the Novel Phytotherapy for the Prevention and Treatment of Serious Diseases

Rafie Hamidpour, Soheila Hamidpour, Mohsen Hamidpour, Mina Shahlari

Department of Herbal Medicine, Pars Bioscience, Leawood, KS, USA.

ABSTRACT

Frankincense (乳香 Rǔ Xiāng; *Boswellia* Species), the resinous extract from the trees of the genus *Boswellia*, has been used for centuries in cultural ceremonies, as a cosmetic agent, and as a traditional medicine to treat a variety of ailments, especially inflammatory diseases including asthma, arthritis, cerebral edema, chronic pain syndrome, chronic bowel diseases, cancer, and some other illnesses. Boswellic acids are the active compounds of frankincense and AKBA (3-*O*-acetyl-11-keto- β -boswellic acid) is the most important and effective acid among them. Some studies have shown that the use of frankincense can also improve the learning and enhance the memory in animals and human beings. It seems that frankincense might have a potential ability to be used as an alternative natural medicine not only for chronic and inflammatory diseases but also for brain and memory disorders.

Key words: Anti-inflammatory, *Boswellia* species, Cancer, Chronic diseases, Memory enhancement

INTRODUCTION

Frankincense (乳香 Rǔ Xiāng; *Boswellia* Species) is a French word, meaning “pure incense.” It is popularly known as Indian olibanum, salai guggal, loban, or kundur. It has been used as an incense, in fumigating preparations for religious rituals and cultural ceremonies, and as a traditional remedy for treating various diseases.^[1] The oleogum resins are secreted by trees of the *Boswellia* species which are tropical, deciduous trees and usually grow as small trees or shrubs with limited natural growing range.^[2] This has been extended by cultivation to meet the worldwide demand.^[3] The resin is obtained by making scrapes in the trunk of the various *Boswellia* species (Burseraceae), and collecting the dried resin

gums from the trees later.^[2,4] Good-quality resin is produced only for 3 years, after which the quality of the collected resin decreases significantly; therefore, the tree should be left to rest for some years after the harvesting period.^[5]

Olibanum is produced mainly by four species from different regions, which are *Boswellia serrata* from India, *Boswellia carterii* from East Africa and China, *Boswellia frereana* from Northeast Africa (Somalia), and *Boswellia sacra* from the Middle East.^[6,7] Today the most traded frankincense is produced in Oman, Yemen, and Somalia.^[3]

Since ancient times, frankincense has been used in many countries such as Africa, China, India, and the Middle East countries for the prevention and treatment of various illnesses, especially chronic inflammatory diseases.^[2,8] In the Indian system of medicine, frankincense (salai guggal) has been used as an anti-in-

Corresponding Author:

Dr. Rafie Hamidpour, Pars Bioscience LLC, 14109 Cambridge Lane, Leawood, KS 66224, USA. Tel: 913-432-0107; Fax: 913-432-5708; E-mail: rafie@parsbioscience.com

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flammatory, anti-arthritic, anti-proliferative, and analgesic agent for the treatment of related diseases.^[9] In Traditional Chinese Medicine (TCM), frankincense of *B. carterii* is commonly used as a remedy for improving the blood circulation and in relieving pain in leprosy, gonorrhoea, and cancer patients.^[10]

In the last decade, the use of olibanum has become more popular in the European countries for the treatment of various chronic inflammatory problems such as arthritis, chronic bowel diseases, asthma, peritumoral brain edema, and other diseases.^[11]

The mechanism of anti-inflammatory activity of the *Boswellia* extract is due to the boswellic acids, which have been identified as the active principle of frankincense. The chemical structure of boswellic acids closely resembles that of steroids,^[9] but their actions are different from painkillers or nonsteroidal anti-inflammatory drugs (NSAIDs) and are related to the component of the immune system and the inhibition of 5-lipoxygenase.^[11]

COMPOSITION

There are many different compounds found in various *Boswellia* species.^[11] The composition of the essential oil and other contents changes from species to species, and differs depending on the climate, harvest conditions, and geographic locations.^[11,12]

Frankincense (乳香 Rǔ Xiāng; *Boswellia* Species) is reported to contain 60-85% resins (mixtures of terpenes), 6-30% gums (mixture of polysaccharides), and 5-9% essential oil.^[13] Resin portion is composed of pentacyclic triterpenes, in which boswellic acid is the active functional group.^[14] Gum portion consists of pentose and hexose sugars with some oxidizing and digestive enzymes. The essential oil is a mixture of monoterpenes, diterpenes, and sesquiterpenes.^[14]

In a study, it was reported that the resinous part of *B. serrata* contains the following: Monoterpenes (α -thujone); diterpenes [macrocyclic diterpenoids such as incensole, incensole oxide, iso-incensole oxide, a diterpene alcohol (serratol)]; triterpenes (such as α - and β -amyrins); pentacyclic triterpenic acids (boswellic acids); and tetracyclic triterpenic acids (tirucall-8,24-dien-21-oic acids).^[5]

Boswellic acids with the molecular formula $C_{32}H_{52}O_4$ form the main active component of frankincense.^[12] The four major boswellic acids (pentacyclic triterpenic acids) found in frankincense are: β -boswellic acid (BA), acetyl- β -boswellic acid (ABA), 11-keto- β -boswellic acid (KBA), and 3-*O*-acetyl-11-keto- β -boswellic acid (AKBA), which have been shown to be responsible for the inhibition of pro-inflammatory enzymes.^[5] Among these four boswellic acids, AKBA is the most important inhibitor of an enzyme called 5-lipoxygenase, which is responsible for inflammation.^[5] AKBA has shown to be effective against a large number of inflammatory diseases such as arthritis, bronchial asthma, chronic colitis, ulcerative colitis (UC), Crohn's disease (CD), and cancer.^[15] The mechanism of action is the binding of AKBA to 5-lipoxygenase in a calcium-dependent and reversible manner, and acts as a non-redox type, non-competitive inhibitor.^[16]

INFLAMMATORY DISEASES

In general, inflammation is the response of the body tissues to irritation, injuries, infections, or disorders of the immune

system (autoimmune diseases), which is characterized by pain, redness, swelling, and sometimes loss of function.^[11]

Leukotrienes are small mediator chemicals produced by the cells of the body, and can cause inflammation by promoting free radical damages, autoimmune responses, cell adhesion, and migration of the cells causing inflammation to the inflamed area.^[17]

Many inflammatory diseases can be caused by leukotrienes, including asthma, colitis, rheumatism, arthritis, and psoriasis.^[17] *Boswellia* has shown to be a specific inhibitor of leukotrienes. It acts by blocking the synthesis of leukotrienes and, therefore, inhibiting inflammation and shrinking the inflamed tissue which is the primary cause of pain and discomfort in many cases.^[17]

Frankincense (乳香 Rǔ Xiāng; *Boswellia* Species) has shown to be effective in treating various inflammatory diseases, and based on data obtained from the experiments done *in vitro* and *in vivo*, boswellic acids are assumed to be the pharmacologically active principles of frankincense which are responsible for the anti-inflammatory and anti-tumorigenic actions.^[18] In a study, it was reported that due to the anti-inflammatory effects of the extracts and powder of frankincense, plaque-induced gingivitis showed improvement of inflammation of periodontium after using the extract and powder of the frankincense.^[19]

HEART DISEASE

Frankincense (乳香 Rǔ Xiāng; *Boswellia* Species), the oleogum resin of *Boswellia* species, has been used in traditional medicine for the treatment of various inflammatory diseases, and today it is used as a complementary and alternative medicine for the treatment of some chronic inflammatory diseases.^[20]

Atherosclerosis is the building up of plaque inside the blood vessels, causing hardening of the arteries. It is the major cause of coronary heart disease and has been found to be linked with inflammation.^[20] Data clearly indicate that AKBA reduces chronic inflammation through the inhibition of nuclear transcription factor-kappa B (NF- κ B), which is a very important factor in the development and progress of chronic inflammatory diseases.^[20] Therefore, therapeutic approaches targeting this transcription factor to treat chronic inflammation in atherosclerosis could be developed.^[20]

ASTHMA

Frankincense (乳香 Rǔ Xiāng; *Boswellia* Species) traditionally has been valued for its effect on the respiratory system, and has been used in steam inhalations, baths, and massages to treat cough, catarrh, bronchitis, and asthma.^[9] Boswellic acids found in frankincense have shown to be responsible for the inhibition of leukotriene biosynthesis and, therefore, can reduce and prevent the inflammation in many chronic inflammatory diseases like asthma.^[21] In a study, several patients with chronic bronchial asthma were treated with the *B. serrata* preparation of 300 mg thrice daily for a 6-week period. The improvement of the disease was obvious in 70% of the patients by disappearance of physical symptoms and signs such as dyspnea (difficulty in breathing), rhonchi (hissing lung sound), and the number of attacks. The data show a definite role of gum resin of *B. serrata* in the treatment of bronchial asthma.^[21]

SKIN

Studies have shown that *B. serrata* extract reduces redness and irritation in the skin and produces an even skin tone.^[22] In China, Frankincense (乳香 Rǔ Xiāng; *Boswellia* Species) has been used as a skin remedy for bruises and infected sores.^[4] The extracts of *Boswellia* family of plants have been found to have a soothing effect on irritated skin, which is due to the pentacyclic triterpene (steroid-like) structure shared in different boswellic acid compounds.^[22]

To allow for easy incorporation of the extract of *Boswellia* containing boswellic acid and its derivatives, the extract needs to be dissolved or dispersed in a suitable carrier such as fatty alcohols or fatty acids, which help to incorporate the extract or acid into compositions suitable for use on skin or hair and improve the stability of products containing the extract.^[22] In addition, AKBA is reported to be an effective topical agent to soften facial lines and relax the skin.^[16]

INFLAMMATORY BOWEL DISEASE

Inflammatory bowel diseases (IBD) refer to the inflammation of intestines and relate to two chronic diseases, UC and CD. Although the exact cause of IBD is still not clear, two factors are considered to be effective in the occurrence of the disease. The first one is the immune dysregulation which is caused by genetic or environmental factors, and the second one is abnormal gastrointestinal (GI) tract luminal factors such as microorganisms of GI tracts, oxidative stress, and defects in the GI mucosal barrier which allow the penetration of luminal factors into mucosa.^[23]

The leukotrienes play an important role in keeping the inflammation active in chronic inflammatory diseases of the colon such as UC. Boswellic acids, which are the active ingredients of the gum resin of *Boswellia* species, have been shown to be specific, non-competitive inhibitors of 5-lipoxygenase, the key enzyme of leukotrienes.^[24,25]

The gum resin of *B. serrata* has been shown to be effective in the treatment of chronic colitis, with a few side effects.^[24] In traditional Iranian medicine (TIM), the oleogum resin of *B. serrata* and *B. carterii* is known for reducing the inflammation and is one of the efficacious remedies for the treatment of IBD. In addition to anti-inflammatory effects, *Boswellia* has been shown to have wound healing, antiulcer, and anti-diarrheal properties.^[23]

A study found that the gum resin of *B. serrata*, at a dosage of 350 mg three times a day over a period of 6 weeks, was effective in inducing remission in about 80% of the patients with ulcer colitis grade II and III. The study reports that even though the effectiveness of Frankincense (乳香 Rǔ Xiāng; *Boswellia* Species) is not better, at least it is similar to the effect of sulfasalazine, a chemical drug used in the treatment of IBD.^[25]

CANCER

Plants are rich sources of antitumor compounds. Oleogum resins from various *Boswellia* species contain triterpenoids with antitumor properties.^[26] In a report, the antitumor activities of

the four triterpenic acids (BA, ABA, KBA, and AKBA) isolated from the gum resin of *B. serrata* were studied and it was found that these acids inhibited the synthesis of DNA, RNA, and protein in human leukemia HL-60 cells in a dose-dependent manner. Among them, AKBA induced the most pronounced inhibitory effect on DNA, RNA, and protein synthesis, in which the effect on DNA synthesis was found to be irreversible. This compound significantly inhibited the cellular growth of HL-60 cells, but did not affect cell viability.^[24]

The studies have shown that boswellic acids are potent apoptotic agents to cancer cells. The boswellic acid acetate seems to induce apoptosis in six human myeloid leukemia cell lines through a caspase-mediated pathway which is activated by the induction of the death receptors 4 and 5 (DR4, DR5).^[27] The anticancer activity of AKBA is attributed to the inhibitory effect on the lipoxygenases, leading to the inhibition of cell proliferation and induction of apoptosis in tumor cells.^[15]

PROSTATE CANCER

It has been shown in several studies that pentacyclic triterpenoids found in *B. serrata* have an inhibitory effect on the growth of prostate cancer cells.^[26] Among the boswellic acids, AKBA inhibits prostate cancer by suppressing vascular endothelial growth factor receptor 2-mediated angiogenesis.^[5] Also, tirucallic acid, isolated from the oleogum resin of *B. carterii*, works as an effective Akt inhibitor, which apply cytotoxic effects in human prostate cancer cell lines *in vitro* and *in vivo*.^[26]

Akt is a serine/threonine protein kinase which has an important role in multiple cellular processes such as cell proliferation, apoptosis, transcription, and cell migration. Akt1 has been associated as a major factor in many types of cancer since it can block apoptosis and promote the survival of the cell.^[26]

BRAIN TUMOR

Brain cancer is a condition in which malignant tumors develop within the brain. These tumors are fast growing and invade the surrounding tissues. Surgical removal of brain tumors is a difficult and detailed procedure, and in many cases, complete removal of the tumor is not possible because of the size, type, and location of the tumor. For these reasons, the average survival of brain tumor patients is only about 9 months even after they are treated with surgery and radiotherapy.^[28] In addition, chemotherapy can prolong the survival of only about 10% of the patients.^[28] In patients with malignant brain tumors, highly active forms of leukotrienes and other inflammatory mediators are produced in the brain and around tumors, causing localized fluid buildups and damages to the healthy nerve cells.^[29]

The anti-inflammatory effect of *B. serrata* has been studied in patients with brain tumors.^[29] An ethanolic extract of the gum resin of *B. serrata* contains boswellic acids. A study has shown that after the application of this preparation (which is called phytopharmacon H15) for a period of 7 days, a reduction of peritumoral brain edema by 22-48% was observed. In contrast to the cells of untreated patients, the cells of the treated tumor tissue showed no

tendency to proliferate within 2 weeks.^[28]

A report on patients with malignant glioma showed that administering 3600 mg/day of *Boswellia* extract (60% boswellic acids), 7 days prior to surgery, caused decrease in the fluid around the tumor to an average of 30% in 8 of the 12 patients and the signs of brain damage decreased during the treatment.^[29] Recently, a detailed study in patients with malignant cerebral tumors who were receiving radiotherapy plus certain amount of *Boswellia* extract showed that after radiotherapy, 75% reduction of cerebral edema was observed in 60% of the patients receiving *Boswellia* extract. The study also showed the ratio of tumor over volume decreased in these patients, suggesting the antitumor effect in addition to the anti-edema activity.^[29]

DIABETES

Boswellia has been known to be effective in a wide variety of diseases, including inflammatory diseases and diabetes mellitus.^[30] A study has shown that oral administration of the aqueous extract of the leaves and roots of *Boswellia glabra* decreased the blood glucose level in diabetic patients. Continuing the use of leaf and root extract for 28 days showed a decrease in serum glucose, cholesterol, triglyceride, urea, and creatinine levels and enzyme activities, in addition to significant hypoglycemic effects.^[30]

Type I diabetes is an autoimmune disease in which a chronic inflammatory process finally causes beta-cell death and insulin deficiency. Extracts from the gum resin of *B. serrata* have been shown to possess anti-inflammatory properties, especially by targeting factors or mediators related to autoimmune diseases.^[31] The study shows that *Boswellia* extract has anti-diabetic effects and could prevent complications of diabetes in the kidneys and liver.^[32]

ANTIMICROBIAL EFFECTS

The essential oil isolated from the oleogum resin of *B. carterii* has been found to have antimicrobial activities against various microorganisms such as fungi, and gram-positive and gram-negative bacterial strains.^[23] In a study, the antibacterial activity of boswellic acids was tested *in vitro* on a group of clinically significant gram-positive and gram-negative bacteria. Among the boswellic acids, AKBA was the most active inhibitor of bacterial pathogens. However, the activity of AKBA was limited to gram-positive bacteria.^[33] The resistance of gram-negative bacteria to lipophilic AKBA might be a result of the presence of lipophilic outer membrane which is composed primarily of lipopolysaccharide molecules and forms a hydrophilic permeability barrier providing protection against the effects of highly hydrophobic compounds.^[33]

Biofilms are a multilayered community of bacterial cells. Staphylococci are known to form biofilms on an implanted medical device or damaged tissues, which are difficult to disrupt. The infections caused by biofilms are difficult to treat due to their inherent antibiotic resistance.^[33] In a study, AKBA was found to effectively inhibit the staphylococcal biofilm and also reduced the performed biofilm of these bacterial pathogens. This report showed that AKBA can prevent as well as reduce the biofilm generation by *Staphylococcus aureus* and *Staphylococcus epidermidis*.^[33] AKBA

was found to be the most active compound against the entire gram-positive bacterial pathogens tested.^[33]

The antimicrobial activity of boswellic acid molecules was studied against the oral cavity pathogens. The results showed that AKBA is the most potent antibacterial compound against all the bacteria tested in this experiment.^[15] AKBA can be used in the development of an antibacterial agent against oral pathogens and can be used in mouthwash for preventing and treating oral infections.^[15]

MEMORY

In traditional medicine, Frankincense (乳香 Rǔ Xiāng; *Boswellia* Species) or olibanum is believed to improve learning and memory on consumption, and it has been used in the elderly for enhancement of memory and in pregnant women to increase the memory and intelligence of their offspring.^[34] The result of a study shows that there is a significant increase in the power of learning at post-learning stage, short-term memory, and long-term memory in rats whose mothers received aqueous extract of *B. serrata* orally during the gestation period.^[35]

Hippocampus is a sensitive region of the brain, which is involved in certain aspects of learning and memory functions.^[36] The dendritic systems are the functional core of neuronal collections as they signify most of the receptive surface of neurons and their organization is essential for integration and transfer of information at the synaptic level.^[36] The study indicated that the young rats whose mothers were treated with *Boswellia* during gestation showed more dendritic branches in CA3 (cornu ammonis) pyramidal neurons.^[36] In an experiment with *Boswellia*-treated young rats prenatally, the CA3 cells showed obvious expansion of their terminal dendritic arborizations, when compared to the control group.^[36] Better learning and memory performance in the offspring of the mothers who consumed frankincense during their pregnancy is related to an increase in the somal volume of hippocampal neurons in cornu ammonis.^[36] These findings suggest that frankincense and its compounds need to be extensively studied in neurophysiology and possibly for the future treatment of neurodegenerative disorders.^[37]

The pharmacological effects of *B. serrata* were studied by its effect on memory deficit in hypothyroid rats.^[34] Many studies have shown that thyroid hormones play a significant role in cell division, maturation, and functioning of mammalian central nervous system. Deficiency of thyroid hormones in the prenatal period can cause growth retardation as well as severe cognitive impairment such as attention, memory processing, and general intelligence deficits.^[34]

In a study in which hypothyroidism was induced by methimazole in adult male Wistar rats, it caused a significant decline in learning and memory. The use of frankincense was found to be effective in preventing this deficiency. This result supports the traditional belief that olibanum has beneficial effect in enhancing memory and learning functions.^[34]

FERTILITY

Fertility regulation with plant preparation has been reported in traditional medicine, and a number of plant species have been

tested for their effects on fertility and some of them have been supported by national and international agencies.^[9] Frankincense (乳香 Rǔ Xiāng; *Boswellia* Species) is used by the Jordanian population as an aphrodisiac and a fertility promoting agent. The gum resin of frankincense contains boswellic acids and other pentacyclic triterpenes, which have a chemical structure similar to that of steroids.^[9] In a study that was conducted to examine the effect of frankincense on the reproductive system and fertility of adult male rats, oral administration of frankincense increased the fertility in rats. In addition, the number of implantations and the number of viable fetuses also increased, which may possibly be due to the increase in sperm motility and sperm density.^[9] The drug may act on the pituitary gland and increase the main hormones of spermatogenesis. Significant increase in the sperm motility of cauda epididymis was observed in the treatment group, which may be due to the effect of frankincense on the enzymes of oxidative phosphorylation.^[9]

In conclusion, frankincense resin is a useful compound in fertility, mainly by its effects on pituitary gland cells. Further studies are needed to identify the specific method of action of frankincense.^[9]

CONTROLLED RELEASE OF DRUGS

Controlled released drug delivery systems are intended to direct the delivery of drugs to targeted tissues in desirable and sustained rates. Among a variety of approaches, preparation of drug-embedded matrix tablets is widely used for this purpose.^[38] Although a wide variety of polymers are used in the matrix tablets for controlling the drug delivery or improving the bioavailability of the contained drug, the need for safe, natural, and effective matrix tablets has always existed.

Olibanum resin is considered suitable for the controlled release of diclofenac over 24 h (once a day administration).^[38] Also, in a study on the controlled release of nifedipine, olibanum and colophony, two natural resins, were used as microencapsulation agents which caused the slow and spread release of the drug over 24 h.^[39]

Olibanum resin is a natural lipophilic polymer which is used as a microencapsulating agent for a good controlled release of the drugs.^[40] The results of studies on the matrix tablets formulated with the use of olibanum resin in several drugs like diclofenac, nifedipine, and carbamazepine have shown that as the concentration of olibanum resin in the matrix tablets was increased, the drug release was decreased,^[38] which means the longer stay of drug in the body.^[39]

PREPARATION AND DOSAGES

Although different methods of preparations can be formulated for oral, rectal, and parenteral administration, the preparations of oral administration are preferred. The pharmaceutical preparations for oral administration may be in the form of tablets or capsules prepared with the use of diluents, such as binding agents, fillers, lubricants, disintegration agents, or wetting agents.^[28]

The compounds can also be formulated for injection, preferably intravenous, intra-arterial, intramuscular, intracranial, intrathecal, or subcutaneous, and can be in unit dosage form, for example, in

ampoules, or in multiple dose containers with the preservative added. The preparations may be in the form of suspensions, solutions, or emulsions in oily or aqueous carriers.^[28]

Boswellia is generally taken orally as a capsule, tablet, or its bark decoction. The standardization of *Boswellia* products is difficult because of the presence of a wide variety of *Boswellia* products.^[5] The suggested dosage for inflammatory or asthmatic conditions is 300-400 mg of the standardized extract (containing 60% boswellic acids) three times daily.^[5]

SAFETY

Frankincense (乳香 Rǔ Xiāng; *Boswellia* Species), the gum resin of *Boswellia*, which has been used as a remedy for thousands of years, has not shown any severe side effect and is considered to be safe.^[25] The anti-inflammatory effects of *Boswellia*, unlike many anti-inflammatory chemical drugs, do not cause any adverse effects on blood pressure, heart rate, respiration, or other autonomic responses, and the resin has remarkably low toxicity.^[17] The gum resin of *Boswellia* is included in the list of safe substances and its use is permitted by US Food and Drug Administration (USFDA) as a food additive.^[15]

Oral preparations of *B. serrata* extract containing AKBA are sold in the market over the counter as anti-inflammatory formulations.^[15] The results of many clinical studies have shown that *Boswellia* is well tolerated in the treatment of rheumatoid arthritis and CD with minimum side effects.^[29]

Taken together, the side effects of frankincense are relatively very less and not severe when compared to the modern drugs and their side effects. Thus, it can be considered quiet safe when taken in the required and therapeutic dosages.

CONCLUSION

Frankincense (乳香 Rǔ Xiāng; *Boswellia* Species) has been used in traditional and modern natural medicine for the treatment of variety of illnesses with very minimal side effects. The anti-inflammatory, anti-arthritis, anti-proliferative, antimicrobial, and analgesic effects of this gum resin can reduce inflammation and pain in the body and relieve the related symptoms of many diseases. The effect of frankincense is remarkable in increasing the number of dendritic segments and branching in the neuron cells of hippocampus, causing more synaptic connections in that area and, therefore, improvement of learning and memory. Extensive studies on frankincense and its effect on neurophysiology could be a right approach in finding a possible new complementary or alternative natural medicine to control, cure, or prevent some kinds of neurodegenerative diseases such as Parkinson's and Alzheimer's.

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