

Boswellia Serrata, A Potential Antiinflammatory Agent: An Overview

M. Z. SIDDIQUI*

Processing and Product Development Division, Indian Institute of Natural Resins and Gums, Namkum, Ranchi-834 010, India

Siddiqui: *Boswellia Serrata*, a Potential Antiinflammatory Agent

The resin of *Boswellia* species has been used as incense in religious and cultural ceremonies and in medicines since time immemorial. *Boswellia serrata* (*Salai/Salai guggul*), is a moderate to large sized branching tree of family Burseraceae (Genus *Boswellia*), grows in dry mountainous regions of India, Northern Africa and Middle East. Oleo gum-resin is tapped from the incision made on the trunk of the tree and is then stored in specially made bamboo basket for removal of oil content and getting the resin solidified. After processing, the gum-resin is then graded according to its flavour, colour, shape and size. In India, the States of Andhra Pradesh, Gujarat, Madhya Pradesh, Jharkhand and Chhattisgarh are the main source of *Boswellia serrata*. Regionally, it is also known by different names. The oleo gum-resins contain 30-60% resin, 5-10% essential oils, which are soluble in the organic solvents, and the rest is made up of polysaccharides. Gum-resin extracts of *Boswellia serrata* have been traditionally used in folk medicine for centuries to treat various chronic inflammatory diseases. The resinous part of *Boswellia serrata* possesses monoterpenes, diterpenes, triterpenes, tetracyclic triterpenic acids and four major pentacyclic triterpenic acids i.e. β -boswellic acid, acetyl- β -boswellic acid, 11-keto- β -boswellic acid and acetyl-11-keto- β -boswellic acid, responsible for inhibition of pro-inflammatory enzymes. Out of these four boswellic acids, acetyl-11-keto- β -boswellic acid is the most potent inhibitor of 5-lipoxygenase, an enzyme responsible for inflammation.

Key words: Agent, antiinflammatory, *Boswellia serrata*, frankincense, olibanum, potential, *Salai/Salai guggul*

Since time immemorial, plants and their products have been the primary resource of food, shelter, clothing, flavors, fragrances as also valuable ingredients for medicines for mankind. In this context, natural resins have played an important role. These have also been used as adhesives, as ingredients for cosmetic preparations, as fragrances in daily rituals and in religious ceremonies, as coating materials and also for their different curative powers^[1-3]. In ancient times, Hindus, Babylonians, Persians, Romans, Chinese and Greeks as well as the people of old American civilizations used natural resins primarily for embalming and for its incense in cultural functions. They firmly believed that when these materials get in contact with fire, the smoke and the fragrance they produce, not only soothe their souls but also please their gods. Burning of these natural resins had become an important component of their cultural life. They burned these resins during sacrificial ceremonies and in their daily rituals to prevent the influence of

evil spirits on their souls or to honour the dead or living ones^[4-6].

Boswellia serrata (*Salai/Salai guggul*) (Family: Burseraceae; Genus: *Boswellia*) is a moderate to large sized branching tree that grows in dry mountainous regions of India, Northern Africa and the Middle East^[7,8]. The family of Burseraceae is represented in the plant kingdom with 17 genera and 600 species wide-spread in all tropical regions. There are about 25 known species belonging to Genus *Boswellia*, most of them occur in Arabia, northeastern coast of Africa and India. Since ancient times, three of these species have been considered as 'true Frankincense' producing trees^[9,10].

Boswellia sacra Flueck, the first species, grows in South Arabia and is known amongst Arabians as 'maghrayt d' sheehaz' and the resin produced is known as 'luban dhakar'. *Boswellia carterii* Birdw, grows in Somalia and in the native language it is called 'moxor' and the resin produced is known as 'luban dhakar'. *Boswellia frereana* Birdw., is

*Address for correspondence

E-mail: mzs_2009@rediffmail.com

also a Somalian species and in the native language it is called 'jagcaar' and the resin produced is known as 'loban majdi' or 'maydi'. This is the most expensive brand of resin in the market^[11]. Another resin producing species is *Boswellia serrata* Roxb., known as 'Indian olibanum', 'Indian frankincense', 'dhup' and 'salai' or 'salai guggul' is found in the middle and northern parts of Eastern India. It has been available as a high quality extract in India for nearly 25 years and marketed under the name *Shallaki*.

In India, the main commercial sources of *Boswellia serrata* are Andhra Pradesh, Gujarat, Madhya Pradesh, Jharkhand and Chhattisgarh. Regionally, it is also known by different names. The botanical origin and vernacular names of *Boswellia serrata* are given in Table 1. *Salai*, an oleo gum-resin, is a plant exudate of genus *Boswellia* (Family: Burseraceae). It is tapped from the incision made on the trunk of the tree, which is then stored in specially made bamboo basket. The semi-solid gum-resin is allowed to remain in the basket for about a month during which its fluid content locally known as 'ras' keeps flowing out. The residue, semi-solid to solid part, is the gum-resin which hardens slowly into amorphous, tear-shaped products with an aromatic scent. Then, it is broken into small pieces by wooden mallet or chopper and during this process all impurities including bark pieces etc. are removed manually. The gum-resin is then graded according to its flavour, colour, shape and size. Generally four grades i.e. Superfine, Grade I, Grade II and Grade III are available in the market. The fresh gum obtained from the tree is hot with pleasant flavour and slightly bitter in taste. It had been the 'frankincense' of ancient Egyptians, Greeks and Romans who used it as prized incense, fumigant as well as a multipurpose aromatic. It is generally used in making incense powder and sticks.

The oleo gum-resins contain 30-60% resin, 5-10% essential oils, which are soluble in the organic

solvents, and the rest is made up of polysaccharides (~ 65% arabinose, galactose, xylose) which are soluble in water^[12-14]. The resins have a fragrant aroma because of the presence of essential oils and this accounts for their commercial importance. The essential oil of gum-resin is one of the most commonly used oils in aromatherapy, paints and varnishes. Pure oleo gum-resin collected in the optimum season hardens slowly, retaining its golden colour and transparency. But the colour varies from golden brown to dark brown or dark greenish-brown depending on the locality, season, size of the tree and the wound-surface, collection process and storage. Darkening of colour of resin is also due to autoxidation, polymerization and enzymatic reactions. The resin is generally harvested all through the summer and autumn after the tree has been wounded in March or April. *Boswellia* tree can produce exudates in good quality only for three years. After this period, the quality of the collected resin decreases considerably. Therefore, the tree should be left to rest for some years after harvesting period.

Historical/traditional applications:

Boswellia serrata is one of the ancient and most valued herbs in Ayurveda. "Gajabhakshya", a Sanskrit name sometimes used for *Boswellia*, suggests that elephants enjoy this herb as a part of their diet^[15]. Three renowned ancient texts form the pillars of classical Ayurvedic Science, which has its roots in India: Charaka's *Charaka Samhita* (c.B.C. 700), the first fundamental medical text; Susruta's *Susruta Samhita* (c.B.C. 600), which attempted to amass the entire medical knowledge, with special focus on surgery; and the two-volume tome comprising *Astanga Samgraha* and *Astanga Hridaya* (c.130-200 A.D.), written by Vagbhata the Elder and Vagbhata the Younger, which synthesized the works of Charaka and Susruta and summarized the eight parts of Ayurveda in prose and verse forms. The first two pillars of Ayurveda describe the antirheumatic

TABLE 1: BOTANICAL ORIGIN AND VERNACULAR NAMES OF BOSWELLIA SERRATA

Botanical origin	Vernacular names
Division: Spermatophyta	English: Indian Olibanum or Indian frankincense
Sub-division: Angiospermae	Hindi: Kundur, <i>Salai</i>
Tribe: Rosopsida	Bengali: Kundur, <i>Salai</i>
Sub-tribe: Rosidae S. lat.	Gujarati: Dhup, Gugali
Over-class: Rutanae	Kannada: Chitta, Guguladhuph
Class: Anacardiales	Malayalam: Parangi, Saambraani
Family: Burseraceae	Tamil: Parangi, Saambraani
Genus: <i>Boswellia</i>	Telugu: Phirangi, Saambraani
Species: <i>serrata</i>	Sanskrit: Ashvmutri, Kundara, Shallaki.

(antiarthritis) activity of *gugguls*-the gum-resins of trees^[16-20]. In addition to its beneficial use for arthritis, this gummy resin is also mentioned in traditional Ayurvedic and Unani texts as an effective remedy for diarrhoea, dysentery, ringworm, boils, fevers (antipyretic), skin and blood diseases, cardiovascular diseases, mouth sores, bad throat, bronchitis, asthma, cough, vaginal discharges, hair-loss, jaundice, hemorrhoids, syphilitic diseases, irregular menses and stimulation of liver. It is also diaphoretic, astringent, diuretic and acts both as internal and external stimulant. Modern medicine and pharmacology strongly point out to its use as an antiarthritic, antiinflammatory, antihyperlipidemic (controls blood lipids), antiatherosclerotic (anticoronary plaque), analgesic (pain-reliever) and hepatoprotective (protects the liver)^[15,21-24].

Composition of *Boswellia serrata* resin:

The resinous part of *Boswellia serrata* contains^[25-31], monoterpenes (α -thujene); 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); tetracyclic triterpenic acids (tirucall-8,24-dien-21-oic acids). The structures of four major pentacyclic triterpenic acids (boswellic acids) as also some of their characteristic features are given in fig. 1 and Table 2, respectively^[32].

In vitro studies and animal models show that boswellic acids were found to inhibit the synthesis of pro-inflammatory enzyme, 5-lipoxygenase (5-LO) including 5-hydroxyeicosatetraenoic acid (5-HETE) and leukotriene B4 (LTB-4), which cause bronchoconstriction, chemotaxis, and increased vascular permeability^[33-38]. Other antiinflammatory plant constituents, such as quercetin, also block this enzyme, but they do so in a more general fashion, as an antioxidant, whereas boswellic acids seem to be specific inhibitor of 5-LO^[39]. 5-LO generates inflammatory leukotrienes, which cause

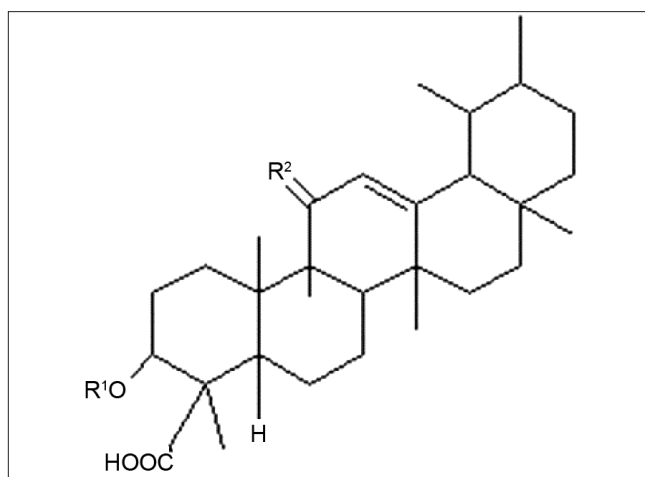


Fig. 1: Structures of four pentacyclic triterpenic acids (Boswellic acids)
 β -Boswellic acid, R₁=H, R₂=H₂; acetyl- β -boswellic acid, R₁=Ac, R₂=H₂;
 11-keto- β -boswellic acid, R₁=H, R₂=O; acetyl-11-keto- β -boswellic acid, R₁=Ac, R₂=O.

TABLE 2: SOME OF THE CHARACTERISTIC FEATURES OF FOUR PENTACYCLIC TRITERPENIC ACIDS (BOSWELLIC ACIDS)

Properties	B-Boswellic acid	Acetyl- β -Boswellic acid	11-keto- β -Boswellic acid	Acetyl-11-keto- β -Boswellic acid
Molecular formula	C ₃₀ H ₄₈ O ₃	C ₃₂ H ₅₀ O ₄	C ₃₀ H ₄₆ O ₄	C ₃₂ H ₄₈ O ₅
Molecular weight	456.7	498.74	470.69	512.73
Chemical name	3 α -Hydroxy-urs-12-en-23-oic acid	3 α -Acetoxy-urs-12-en-23-oic acid	3 α -Hydroxy-urs-12-en-11-keto-23-oic acid	3 α -Acetoxy-urs-12-en-11-keto-23-oic acid
Melting point	226-228°	252-255°	195-197°	271-274°
Specific rotation	+106.8°	+138°	+78.5°	+88.5°
UV-MeOH	Maxima at 208 nm	Maxima at 208 nm	Maxima at 250 nm	Maxima at 250 nm
NMR (in CDCl ₃ , δ ppm)	5.15, CH=C; 4.08, CH-OH; 2.3-1.1, Methylenes and methines, 23 protons; 1.1-0.7 Methyls, 21 protons	5.31, CH=C; 5.2, CH-OAc; 2.1, COCH ₃ ; 1.9-1.25, Methylenes and methines 23 protons; 1.2-0.7, Methyls 21 protons	5.55, CH=C; 4.08, CH-OH; 2.6-1.4, Methylenes and methines 21 protons; 1.25-0.75, Methyls 21 protons	5.55, CH=C; 5.2, CH-OAc; 2.6-1.4, Methylenes and methines 21 protons; 1.25-0.75, Methyls 21 protons
FTIR (in KBr, cm ⁻¹)	3500 (OH), 1699.5 (COOH)	1732 (OAc), 1701 (COOH)	3460 (OH), 1693 (COOH)	1740 (Ac), 1701 (COOH), 647(α,β -unsaturated carbonyl).
GC-MS	394 (M-68[44 due to -CO ₂ and 18 due to -H ₂ O]); Other fragments: 203, 189, 175, 161.	394 (M-104[44 due to -CO ₂ and 60 due to -HOAc]); 218 (base peak)	408 (M-68[44 due to -CO ₂ and 18 due to -H ₂ O]); 232 (base peak); Other fragments: 217, 175, 161, 135	408 (M-68[44 due to -CO ₂ and 18 due to -HOAc]); 232 (base peak); Other fragments: 217, 175, 161, 135

inflammation by promoting free radical damage, calcium dislocation, cell-adhesion and migration of inflammation-producing cells to the inflamed body area. In contrast to non-steroidal antiinflammatory drugs (NSAIDs), which are well known to disrupt glycosaminoglycan synthesis, thus accelerating articular damage in arthritic conditions, boswellic acids have been shown to significantly reduce glycosaminoglycan degradation^[40-43]. *In vivo* study examining the effect of *Boswellia* extract and ketoprofen on glycosaminoglycan metabolism showed that *Boswellia* considerably reduced the degradation of glycosaminoglycans compared to controls, whereas ketoprofen caused a reduction in total tissue glycosaminoglycan content^[44].

In vitro studies by Ammon *et al.* in 1993 also elucidated that boswellic acids were found to inhibit leukotriene synthesis via 5-LO, but did not affect the 12-lipoxygenase or cyclooxygenase activities, nor did they prevent peroxidation of arachidonic acid by iron or ascorbate. Boswellic acids were, therefore, shown to be specific, non-redox inhibitors of leukotriene synthesis, either interacting directly with 5-LO or blocking its translocation^[45,46]. Boswellic acids have also been observed to inhibit human leukocyte elastase (HLE), which may be involved in the pathogenesis of emphysema. HLE also stimulates mucus secretion and thus may play a role in cystic fibrosis, chronic bronchitis and acute respiratory distress syndrome^[47,48]. HLE is a serine protease, which initiates injury to the tissues which, in turn, triggers the inflammatory process. This dual inhibitory action on the inflammatory process is unique to boswellic acids. Of these four boswellic acids, 3-acetyl-11-keto- β -boswellic acid (AKBA) is the most potent inhibitor of 5-LO, an enzyme responsible for inflammation.

Singh *et al.*^[49] studied the antiinflammatory activity of mixture of boswellic acids and observed 25-46% inhibition of paw oedema in rats and mice. They have also reported that in chronic test of formaldehyde arthritis it exhibited 45-67% antiarthritic activity in a similar dose range. The fraction was effective in both adjuvant arthritis (35-59%) as well as established arthritis (54-84%). It also showed antipyretic effect, with no ulcerogenic effect. Kulkarni *et al.* and Chopra *et al.* have reported clinical trials of *Boswellia*'s antiinflammatory properties in combination with *Withania somnifera*, *Zingiber officinale* and

Curcuma longa and the isolated effects of *Boswellia* on rheumatoid arthritis could not be revealed^[50,51]. However, the clinical trials of gum-resin of *Boswellia* alone have shown to improve symptoms in patients with osteoarthritis, and rheumatoid arthritis^[52,53]. The boswellic acid from *Boswellia serrata*, when tested on new model i.e. Papaya Latex Model, showed significant activity of mean 35% inhibition of inflammation. Since the new model is reported to be sensitive to slowly acting remission-inducing drugs, its effectiveness on boswellic acid throws some light on its mechanism of action, which seems to be unlike aspirin and steroidal drugs^[54]. Poeckel and Werz in 2006 have summarized the biological actions of boswellic acids on the cellular and molecular level and attempted to put the data into the perspectives of the beneficial effects manifested in animal studies and trials with human subjects related to inflammation and cancer^[55]. Sharma *et al.*^[56] have reported the effect of boswellic acids on bovine serum albumin (BSA)-induced arthritis in rabbits.

Gayathri *et al.*^[57] in 2007 have reported that pure compound from *Boswellia serrata* extract exhibits antiinflammatory property in human peripheral blood mononuclear cells (PBMCs) and mouse macrophages through inhibition of tumor necrosis factor-alpha (TNF-alpha), interleukin-1beta (IL-1beta), NO and mitogen activated protein (MAP) kinases. Incensole acetate, a novel antiinflammatory compound isolated from *Boswellia* resin inhibits nuclear factor-kappa B activation^[58]. Boswellic acids are direct 5-LO inhibitors that efficiently suppress 5-LO product synthesis in common *in vitro* test models. However, the pharmacological relevance of such interference *in vivo* seems questionable^[59]. Acetyl-11-keto- β -boswellic acid inhibits prostate tumor growth by suppressing vascular endothelial growth factor receptor 2- mediated angiogenesis^[60].

A clinical trial conducted by Raychaudhuri and co-workers in India has shown that the extract of the plant, *Boswellia serrata*, can reduce pain and considerably improve knee-joint functions, in some cases providing relief even within seven days. Raychaudhuri and her colleagues described their study as the first to evaluate the efficacy of the extract enriched with a form of boswellic acid on osteoarthritis^[61]. Very recently, Pawar *et al.* in 2011 have reported a simple, rapid, accurate,

reproducible, selective and economic HPTLC method for routine quality control analysis as also quantitative determination of β -boswellic acid from *Boswellia serrata* Roxb. (exudate) and its formulations^[62].

Dosage:

Boswellia is generally taken as a capsule, tablet or its bark decoction orally. The recommended dosage is based on historical practice or available trials. Presently, it is not clear what the optimal dose is to balance safety and efficacy. The manufacturing of *Boswellia* products varies from one produce to the other and this makes it even more difficult for standardization to happen. It is important to note that most of the trials used various products made by various manufacturers, so clinical effects may not be comparable^[63,64].

Branded Formulations containing *Boswellia serrata*:

Besides its use in religious ceremonies, olibanum has been utilised as an important fixative in perfumes, soaps, creams, lotions and detergents, with an oriental note in its scent, in leading products of the perfume and cosmetic industry. The interest of pharmaceutical companies created a third market for olibanum. Since ancient times, it has been used in folk medicines for its antiseptic, antiarthritic and antiinflammatory effects. For this reason, in the last 20 years olibanum has gained increasing attention from scientists to better define its medicinal effects and identify the constituents responsible for these effects. Therefore, primary aim should be to find out a rapid way of distinguishing the different types of olibanum from each other and to identify the diagnostic markers for each species. This discrimination is important to improve the quality of the products obtained from olibanum, like its essential oil or the phytopharmaceuticals prepared from the resin acids. Even from an economical point of view, this identification is necessary for satisfaction of the consumer. Some of the branded formulations containing *Boswellia serrata* available in the market are:-

Boswellin[®], a registered trademark by Sabinsa Corporation, introduced to the US and European markets in 1991. This is available in capsules or tablets, and also in a soothing pain relieving cream containing capsaicin. Products containing boswellic acids range from 150-250 mgs/capsules or tablets, and are taken orally two to three times a day.

Shallaki[®], contains 125 mg *Boswellia serrata* in each capsule manufactured by Himalayan Drug Company, Makali, Bangalore, as Licensed User of the Trade Mark owned by MMI Corporation, has excellent antiinflammatory and analgesic properties, useful in relieving joint-pains. 60 capsule costs Rs. 75/- and the dose is 1 capsule twice daily (Batch No. F297001G). The website of the company is www.himalayahealthcare.com.

Niltan[®], is a cream in a 15 g tube for external application. Manufactured by Dr. Reddy's Laboratories Limited, Hyderabad, it is a combination of active herbal extracts (boswellin, arbutin, liquorice extract and coriander seed oil in a cream base). It reduces the activity of the enzyme tyrosinase within the skin, thus diminishing the production of melanin, which results in the reduction of dark skin formation.

Rheumatic-X[®], contains 20 mg 'Shallaki' besides a number of ingredients, manufactured by Sunrise Herbals, Varanasi (U.P., India), meant for rheumatoid, gouty, osteoarthritis and sciatic pain, two capsules twice daily or as directed by the physician.

CONCLUSIONS

The resin of *Boswellia* species ('frankincense', 'olibanum') has been used as incense in religious and cultural ceremonies since time immemorial. Its medicinal properties are also widely recognized, mainly for the treatment of inflammatory conditions, as well as in some cancerous diseases, wound healing and its antimicrobial activity. Despite its historical, religious, cultural and medicinal importance, *Boswellia* has not been thoroughly studied, and gaps still exist between our knowledge of the traditional uses of the resin and the scientific data available.

Traditional system of medicine continues to be widely practised for various reasons. Fast population-growth, inadequate supply of branded medicines, alarmingly prohibitive cost of treatment, adverse side-effects of several allopathic drugs and ever-increasing resistance to current drugs for infectious diseases have led to growing emphasis on the use of plant-materials as a source of medicines for a wide variety of human ailments. However, a sustained and uninterrupted supply of the source-materials often becomes difficult due to various factors like environmental variations, local cultural practices,

diverse geographical distribution, increasing labour-cost, non-selection/improper selection of the suitable plant-stock and prevalent exploitative practices by pharmaceutical industry. A fully integrated approach for the cultivation, conservation and preservation of important plant-species through plant molecular biology, plant-tissue culture techniques, both extensive and intensive research on the rationality and methodology of Ayurvedic practices, isolation of the active constituents and their development into new therapeutics, standardization and validation of known herbal medicines and other related aspects need to be continuously focused upon. In fact, the time has come when our medicinal discoveries must move in mighty leaps and bounds, if the human race is to be saved from the onslaughts of continuously multiplying maladies.

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