

BOSWELLIA SERRATA RESIN ISOLATES: CHEMICAL COMPOSITION AND PHARMACOLOGICAL ACTIVITIES

Natalija G. Tošić*, Vesna D. Nikolić, Vojkan M. Miljković, Ljubiša B. Nikolić

Faculty of Technology, University of Niš, Leskovac, Serbia

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Frankincense is an aromatic resin obtained from a tree of various species of the genus *Boswellia*, family *Burseraceae*. *Boswellia serrata*, which is characteristic for the Indian subcontinent and whose pharmacological effects have been proven in numerous studies, has the greatest medical importance. The aim of this paper is a detailed literature review of the chemical composition and biological activity of Indian frankincense resin isolates (*B. serrata*). In vitro studies and numerous clinical trials have shown promising beneficial effects in the treatment of inflammatory diseases, such as rheumatoid arthritis, ulcerative colitis, inflammatory bowel disease (ileitis), Crohn's disease and asthma, as well as in the reduction of peritumoral edema. The resin obtained from *B. serrata* which has both religious and medical significance is today widely used in the cosmetics industry due to its high content of essential oil.

Keywords: *Boswellia serrata*, frankincense, boswellic acid, resin, essential oil

Introduction

The genus *Boswellia* consists of 21 species which grow throughout Africa and South Asia, as well as in the Arabian Peninsula [1]. The most important species of this genus are *Boswellia sacra* (Oman and Yemen), *Boswellia serrata* (India), *Boswellia ovalifoliolata* (India), *Boswellia pirottae* (Ethiopia), *Boswellia carterii* (Somalia), *Boswellia frereana* (Somalia), *Boswellia dalzielii* (West Africa), *Boswellia neglecta* (Ethiopia and Somalia), *Boswellia rivae* (Ethiopia and Somalia), *Boswellia papyrifera* (Ethiopia and Sudan), *Boswellia popoviana* (Yemen), *Boswellia nana* (Yemen), *Boswellia dioscorides* (Yemen), *Boswellia bullata* (Yemen), *Boswellia elongate* (Yemen), *Boswellia ameero* (Yemen), *Boswellia socotrana* (Yemen), *Boswellia globosa* (Somalia), *Boswellia ogadensis* (Ethiopia), *Boswellia odorata* (Niger, Nigeria and Cameroon), *Boswellia madagaskariensis* (Madagascar) [2].

The ancient Egyptians inflamed frankincense in religious ceremonies and rituals. It was used to mummify and embalm the bodies. In addition to the Egyptians, frankincense was also used by the Assyrians, Babylonians, Greeks and Romans. The Romans inflamed large quantities of frankincense on victory parades and for war triumphs. Frankincense has an important place in Christianity (it is mentioned 22 times in the Bible). It was one of the most valued and expensive substances in the ancient world; while in Judaism it was one of the four sweet fragrances used in Jewish temples [3].

The chemical composition of resin from species of

Boswellia depends on the geographical location and climatic conditions as well as on the fact when collection of resin is done [4]. The presence of boswellic acid in almost all species is the main characteristic of this genus [5].

The resins obtained from different species of *Boswellia* differ in the composition of biologically active compounds (boswellic acid, essential oil, polysaccharides). Studies show that the resin of Indian frankincense (*B. serrata*) contains similar amounts of acetyl-11-keto- β -boswellic acid (AKBA) (2.2–2.9%) and 11-keto- β -boswellic acid KBA (3.0–4.7%), while the resin of African frankincense (*B. carterii*) contains significantly less KBA (0.5%) [6]. Biologically active components isolated from the resin and the essential oil of the genus *Boswellia* are: Incensole, incensyl acetate, β -amyrin, β -amyrenone, α -amyrin, α -amyrenone, 24-noroleana-3,12-diene, 24-norursa-3,12-diene, lupeolic acid, acetyl lupeolic acid and boswellic acids (11-keto- β -boswellic acid, α -boswellic acid, 3-O-acetyl- α -boswellic acid, acetyl- β -boswellic acid, acetyl-11-keto- β -boswellic acid), α -thujene, α -pinene, camphene, thujadiene, sabinene, β -pinene, β -mircene, *n*-decane, *n*-dodecane, *n*-undecane, *n*-tridecane, *n*-tetradecane, 3-carene, *p*-cymene, limonene, eucalyptole, *cis*-sabinene hydrate, terpinolene, *p*-cymene, linalool, fenchone, α -campholenol, *trans*-pinocarveol, *cis*-verbenol, *cis*-sabinol, pinocarvone, 4-terpineol, *p*-cycym-ol, α -terpineol, verbenone, *trans*-carveol, bornyl acetate, thymol, carvacrol, β -elemene, β -caryophyllene,

* Author address: Natalija G. Tošić, Faculty of Technology, University of Niš,

Bulevar oslobođenja 124, 16000 Leskovac, Serbia

e-mail address: natalija170394@gmail.com

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α -copamene, β -bourbonene, *n*-nonane, tricyclene [7].

From the medical aspect, *B. serrata* is of the greatest importance (Fig.1), and further in this paper, the chemical composition and biological activities of different isolates of this species are presented in detail.



Figure 1. Frankincense (*B.serrata*) - the resin

Chemical composition of the *B. serrata* resin

The resin obtained from the wood of *B. serrata* is a complex mixture of terpenoids and sugars and contains more than 200 different substances: polysaccharides, proteins, terpenoids, inorganic compounds and essential oil [8]. Depending on the origin and the period of collection, the resin contains 8-12% of essential oil, 45-60% of polysaccharides and 25-35% of higher terpenoids [9, 10]. The main components of the resin can be divided into three groups: volatile oils or lower terpenoids, higher terpenoids and carbohydrates.

The composition of volatile oils and lower terpenoids varies depending on the age and quality of the resin. The GC/MS analysis showed that the fraction of essential oil from *B. serrata* extracted with *n*-hexane contains esters (62,1%), alcohols (15,4%), monoterpenes (9,9%) and diterpenes (7,1%) [11].

Higher terpenoids are one of the main components of *B. serrata* wood resin (25-35%), which contains mainly β -boswellic acid (BA), acetyl- β -boswellic acid (ABA), KBA, and AKBA [5].

The main fraction of the resin are carbohydrates which represent the quantity of 45-60%. The results about the presence of disaccharides, oligo- and polysaccharides have been published. There are not enough detailed studies in the literature on the composition of polysaccharides present in the resin. Hexuronic acid, arabinose and galactose are also present in frankincense resin [12].

Extracts of resin

For the extraction of pharmacologically active ingredients from frankincense resin different methods have

been documented (Table 2). The choice of extraction method depends on the structure of the drug, technological capabilities, physico-chemical characteristics and stability of the active substance. The most commonly used methods are maceration, percolation, Soxhlet extraction, microwave-assisted extraction, ultrasonic extraction, supercritical fluid extraction and various distillation methods for subsequent processing of the obtained extracts.

Table 1. The extraction techniques and operating conditions for active ingredients from frankincense resin [13]

Extraction technique	Solvent	Condition	Active constituent	Max. yield
Three-phase partitioning	<i>t</i> -butanol	3-4 h	Acetyl keto-boswellic acid	35-40%
	dichloromethane			
Percolation	Ethanol,	50-1000 ml	Boswellic acid	25-30%
	petrolether,	solvent used		
	water, acetone, methanol	24 h		
Ultrasonic assisted	Petrolether, ethanol, methanol	50-300 ml	Acetyl keto-boswellic acid	40-60%
		solvent, 2-3 h		
		20-25 kHz, 150-200 W		
Supercritical fluid extraction	Carbon dioxide	100-125 bars	Boswellic acid	45-50%
		40 – 45 °C		
Soxhlet extraction	Ethanol, hydroalcohols, petrolether, hexane, methanol,	40-70 °C,	Carbohydrates, tannins, glycoside terpenes	45-55%
		10-24 h		
		300-500 ml		
Hydrodistillation	Distilled water	3-8 h,	Essential oil	5-10%
		160 °C		
Maceration	Water, ethanol, hydroalcohols	1:1 ration,	Boswellic acid	/
		6-12 h		
Microwave-assisted	Water	8-10 h	Essential oil	2-5%
		1 dm ³		
Steam distillation	Distilled water	100 °C	Boswellic acid	3-10%

In the last two decades, extracts of resin obtained from the tree of *B. serrata* have become increasingly popular in the Western world [6]. Standardized preparations of Indian frankincense extracts are commercially available and used to treat inflammatory diseases [14]. Among boswellic acids, the two most active and promising anti-inflammatory agents are AKBA and KBA [15].

Boswellic acids

Boswellic acids are pentacyclic triterpenes that are known as bioactive and responsible for most of the therapeutic effects. These acids exist as α -configuration and β -configuration. Numerous pharmacological studies indicate that β -configuration derivatives are more active than α -analogues [16].

Structural formulas of different boswellic acids are shown in Figure 2.

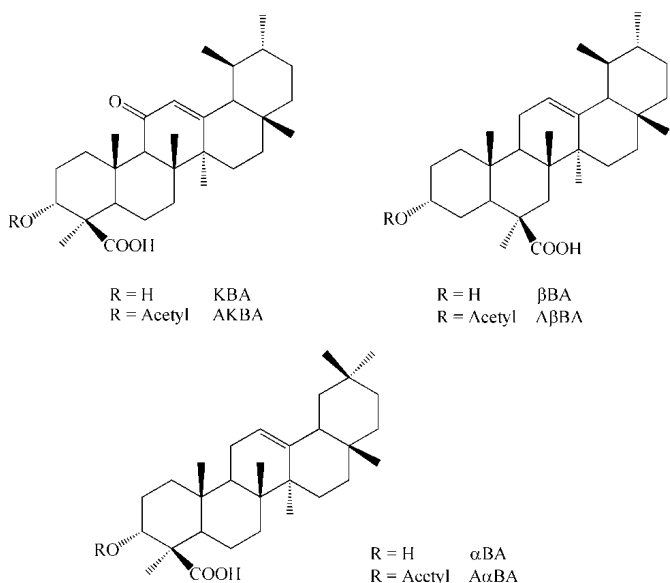


Figure 2. Structures of different boswellic acids. α BA – α -boswellic acid; β BA – β -boswellic acid; $\Delta\alpha$ BA – acetyl- α -boswellic acid; $\Delta\beta$ BA – acetyl- β -boswellic acid; AKBA – acetyl-11-keto- β -boswellic acid; KBA – 11-keto- β -boswellic acid [6]

An important advantage of boswellic acid derivatives is their lipophilicity, which allows them to pass through the blood-brain barrier, and therefore have the potential in the treatment of central nervous system (CNS) malignancies. In this regard, *in vitro* studies have shown inhibitory effects on gliomas and a better effect compared to clinically used etoposide and camptothecin [17, 18]. These findings led to the first clinical trials of this group of chemical compounds, boswellic acids. So far, steroid drugs have been necessary to control cerebral edema. However, steroid therapy has numerous side effects including immunosuppression, osteoporosis and Cushing's syndrome. Also, these drugs reduce the effectiveness of chemotherapy by reducing tumor perfusion and inhibiting apoptosis of malignant glioma cells. Boswellic acid derivatives are suitable for the palliative treatment of brain tumors, primarily because of the proven anti-edematous effect [17, 18]. Also, *in vitro* studies confirm that boswellic acid isolated from the resin of frankincense inhibits the synthesis of proinflammatory products of 5-lipoxygenase (5-LOX), including 5-hydroxyicosatetraenoic acid and leukotriene B₄ [19], which is considered to be the main mechanism of anti-inflammatory effect. The attention of the scientific community was attracted by the inhibitory effect of boswellic acid on 5-LOX which leads to reduced leukotriene production because various chronic inflammatory diseases are associated with increased leukotriene activity [20].

Boswellic acids and triterpenoids derived from the resin of *B. serrata* tree have an inhibitory and apoptotic effect on the growth of HL-60 leukemia cells [21].

Mechanism of action of boswellic acids

BA modify the activity of different target compounds,

including 5-LOX, leukocyte elastase, topoisomerase and C2 convertase.

5- LOX inhibition

In neutrophils, the enzyme 5-LOX is dominant in the conversion of endogenous arachidonic acid to 5-hydroxyicosatetraenoic acid (5-HETE) and leukotrienes. The effect is vasoconstriction, bronchospasm and chemotaxis. Boswellic acids in a dose-dependent relation inhibit the key enzyme for leukotriene synthesis, LOX, in rat peritoneal neutrophils [22, 23]. Of the boswellic acids, AKBA has proven to be the most powerful inhibitor of 5-LOX.

Inhibition of leukocyte elastase

It is known that boswellic acids inhibit human leukocyte elastase activity (eng. human leukocyte elastase, HLE) [24]. HLE has an influence on several diseases, including pulmonary emphysema, cystic fibrosis, chronic bronchitis, and acute respiratory distress syndrome. Inhibition of HLE has been demonstrated for many lipophilic compounds, but the dual inhibitory activity of 5-LOX and HLE is unique for pentacyclic triterpenes. The levels of leukotriene and HLE increase in many inflammatory diseases, so boswellic acid derivatives, such as AKBA, may be important in such pathophysiological processes [25].

Inhibition of topoisomerase

Boswellic acids have a dual catalytic inhibitory action on human topoisomerase (I and II α). Boswellic acids not only inhibit DNA synthesis in promyelocytic leukemia cells depending on the dosage but also, inhibit topoisomerase (I and II α) by competing with DNA for enzyme binding [19, 24, 26].

Inhibition of C2 convertase

Boswellic acid inhibits C2 convertase, which plays an important role in the classical complement pathway for specific immunity [27].

Pharmacokinetic properties of boswellic acids

As high lipophilic, KBA and AKBA have relatively poor absorption through the gastrointestinal tract, but high retention [6, 28]. A prerequisite for good absorption is sufficient solubility in intestinal fluid, which depends on the drug formulation and the composition of intestinal fluid. The half-life ($t_{1/2}$) of KBA is approximately 6 h. This indicates that BA should be taken per os every 6 h to reach maximum plasma levels [29]. Also, it was determined that BA should be taken at the same time as fatty meals because their concentration in plasma significantly increases that way [22]. Sharma et al. (2010) used complexation to enhance the pharmacokinetic profile of BA, particularly poor absorption through the gastrointestinal tract in order to achieve better bioavailability. Absorption was enhanced by complexing BA with phosphatidylcholine. Due to improved pharmacokinetic properties and bioavailability, the phosphatidylcholine complex showed

better anti-inflammatory and hypolipidemic activity compared to uncomplexed BA [30].

Application and usage of frankincense resin

Frankincense has been used in traditional medicine in China, India and Africa for centuries. The resin obtained from the *B. sacra* tree is used today in dental infections. It is also used for problems with the digestive tract, to relieve muscle and joint pain, fever, asthma, colds and coughs [31]. Burning frankincense is used to reduce pain in general and as an expectorant. Likewise, *B. dalzielii* Hutch. is effective in the treatment of ulcers, tetanus, skin diseases, internal bleeding, rheumatism, fever, and digestive disorders, as well as for the treatment of snake bites [32]. In traditional medicine, *B. serrata* Roxb. is used in the treatment of asthma, ulcers, dysentery, rheumatism, hemorrhoids, urinary tract diseases, chronic diarrhea, gout, cystic breasts, tumors and gonorrhea [33]. Traditionally, frankincense obtained from the tree of *B. carterii* is used in inflammatory diseases, ie. Crohn's disease and ulcerative colitis [34], and in Chinese folk medicine to relieve pain caused by leprosy, gonorrhea, tumors, as an astringent [35].

Clinical indications for the application of *B. serrata* resin extract

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with a high prevalence of cardiovascular and gastrointestinal side effects. More recently, selective inhibitors of cyclooxygenase (COX-2) have been developed to improve the profile related to side effects [36]. However, some serious cardiovascular side effects have reduced initial enthusiasm for these new anti-inflammatory drugs [37, 38]. In the last two decades, preparations of resin obtained from *B. serrata* and other *Boswellia* species have gained on popularity in Western countries. Experiments on animals and clinical pilot trials support the affirmation about resin extracts as the compound with a potential in treatment of various inflammatory diseases. Compared to NSAIDs, *B. serrata* resin extract (BSE) is expected to have better tolerability and fewer side effects, which needs to be confirmed in further clinical trials [6].

BSE is widely used as an adjunction in the treatment of inflammatory diseases such as rheumatoid arthritis, Crohn's disease, ulcerative colitis and inflammatory bowel disease [39]. Several clinical trials suggest promising benefits, without serious long-term and irreversible side effects [6]. BSE is used as a compound with a potential in the treatment of Crohn's disease and ulcerative colitis, for which no effective cure has been found so far.

Ulcerative Colitis

Leukotrienes have an important role in the inflammatory process of ulcerative colitis. *Boswellia* extract (300 mg three times a day) was compared with sulfasalazine (1 g three times a day) in patients with ulcerative colitis. A benefit was confirmed in patients taking *B. serrata* resin

extract compared to patients on sulfasalazine [40].

Asthma

In a study on the effects of *Boswellia* resin extract on bronchial asthma, 40 patients took 300 mg of the extract three times a day for six weeks, while another group of subjects, 40 patients, received a placebo. In 70% of the patients taking the extract there was a significant improvement, while in 20% of patients receiving placebo a positive effect was confirmed [41]. The Boswellic acids, as higher terpenoids, are responsible for inhibiting leukotriene biosynthesis, and therefore, they reduce/prevent inflammation in many chronic inflammatory diseases such as asthma [42].

Anticancer activity

Malignant neoplasm, or cancer, is a disease in which there is uncontrolled deranged growth and excessive spread of cells, as a consequence of damaged DNA [43]. In the last few decades the risk of cancer has been rising. It has been shown that the ethanolic extract obtained from the resin of *B. serrata* induces apoptosis in brain tumor cells and leukemia and acts as a potent antiproliferative agent [44]. The BSE containing 60% boswellic acid inhibits inflammation and tumors in mice [45]. When HL-60 cells were treated with AKBA, significant morphological changes occurred, which indicates that the cells underwent apoptosis. In vitro, BA, ABA, KBA and AKBA inhibit DNA, RNA, and protein synthesis in HL-60 human leukemia cells in a dose-dependent relation. The effect on DNA synthesis was found to be irreversible [17, 21].

BA, KBA and AKBA showed the antiproliferative and apoptotic effects on NT-29 cells of colon cancer [46, 47], and the caspase-8 activation pathway leading to programmed cell death [48, 49, 50].

Hypolipidemic activity

Based on the results from scientific studies and research done over the past few decades, frankincense can be used as an effective hypolipidemic agent. Aqueous extract obtained from the resin of *B. serrata* reduces total cholesterol (38-48%) and increases HDL (22-30%) in rats on an atherogenic diet, showing hypolipidemic potential [51].

Hepatoprotective activity

Hepatoprotective activity is a result of inhibition of 5-LOX [52]. Zaitone et al. (2015) have proven the protective effect of BA in a non-alcoholic fatty liver disease caused by food intake (non-alcoholic fatty liver disease, NAFLD) in rodents. NAFLD is related to insulin resistance, oxidative stress and cytokine imbalance. Steatosis (fatty liver) and inflammation (NAFLD) were induced in rats by food intake, containing increased fat content, over the period of 3 months. Rats treated with BA (125 or 250 mg/kg of body weight) or pioglitazone showed increased sensitivity to insulin and decreased liver parameters, liver enzyme activity, serum TNF- α (tumor necrosis

factor- α) and IL-6 (interleukin-6) as well as expression of iNOS (inducible nitric oxide synthase) compared to the control group. These studies have shown that boswellic acids are promising agents in clinical treatments [53].

Antidiarrheal activity

The extract of *B. serrata* resin has been shown to be effective in treating diarrhea, without causing constipation in patients with inflammatory bowel syndrome. It has also been found that it is effective against acetylcholine and barium-chloride induced diarrhea by inhibiting the contraction of intestinal smooth muscles [54].

Diuretic activity

The aqueous extract obtained from *B. serrata* resin in a dose of 50 mg/kg of body weight showed a significant diuretic effect in experimental albino mice. When administered intraperitoneal, the aqueous extract enhances sodium and potassium excretion. Also, the extract showed no acute toxicity in a dose of 3000 mg/kg of body weight [55].

Antimicrobial activity

There is a study where the antimicrobial activity of boswellic acids against microbes, which are part of mouth flora, was investigated. AKBA showed an inhibitory effect against all tested pathogens (MIC=2-4 $\mu\text{g/ml}$). The results of this study suggest that AKBA can be used as a drug candidate because of its anti-infective effect against oral pathogens [56]. In another study, the antibacterial effect of boswellic acids on Gram-positive and Gram-negative bacteria was tested. It has been shown that AKBA is the most promising antibacterial agent among all boswellic acids, but the antibacterial spectrum was limited to Gram-positive bacteria only [56].

Hypoglycemic effects

Diabetes mellitus is a metabolic disease in which hyperglycemia and hyperlipidemia are the main disorders. A special Committee of experts has proposed that diabetes mellitus can be classified into four categories: insulin-dependent diabetes (type 1), insulin-independent diabetes (type 2), gestational diabetes (type 4) and other types (type 3) [57].

In type 1 diabetes, the destruction of the β -cells of the pancreas occurs. External agents that can induce β -cell damaging are: viruses (*Mumps*, *Rubella*, *Coxsackie B4*), toxic chemicals and cytotoxic agents [58]. Insulin secretion disorder is accompanied by inflammation of the Langerhans cells of pancreas (insulinitis) where, due to immune system disorders (autoimmune diabetes), invasion of T lymphocytes and macrophages destroys insulin-producing β -cells leading to diabetes type 1. The cause of type 2 diabetes is insulin resistance, which is preceded or frequently accompanied by increased body weight, reduced physical activity, stress, smoking, as well as genetic predisposition [58].

In both autoimmune and type 2 diabetes, proinflam-

matory cytokines play an important role in the pathogenesis of this disease.

The treatment of diabetes includes physical activity, a change of diet, oral antidiabetics, as well as insulin therapy. However, antidiabetics such as biguanides and sulfonylurea derivatives have numerous side effects including hepatotoxicity, coagulation disorder and hypoglycaemia [59]. In the last few decades, the usage of medicinal herbs has increased due to a variety of active ingredients and fewer side effects.

Many researchers have shown the hypoglycemic effect of the extract of *B. serrata* resin. One study showed that supplementation with frankincense resin isolates in a period of six weeks, in patients with type 2 diabetes, lowers fasting glucose levels and increases insulin levels [60].

Currently, there is no effective treatment for type 1 autoimmune diabetes and insulin resistance related to suppression of proinflammatory cytokines and tolerance in patients. Recently, it has been found that the extract of resin of the genus *Boswellia* and some of its pharmacologically active ingredients, especially β -boswellic acids, which play an important role in the suppression of proinflammatory cytokines, have that kind of effect [61].

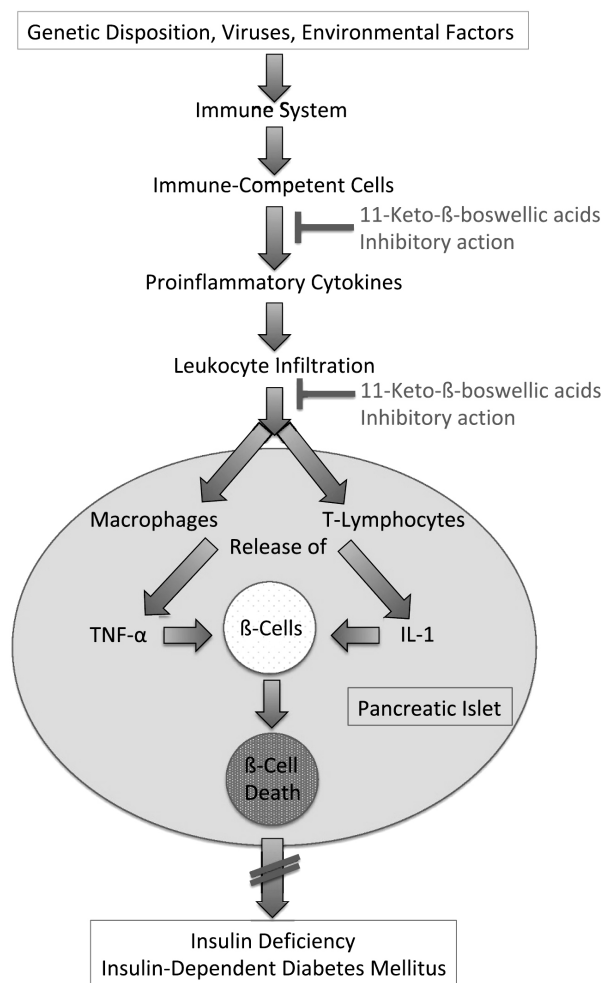


Figure 3. Pathogenesis of autoimmune diabetes [62]

Considering the role of proinflammatory cytokines in type 1 diabetes, as well as the fact that extracts of genus *Boswellia* and some boswellic acids prevent insulinitis, by inhibiting the action of proinflammatory cytokines (Figure 3) and the ability of β -cell to regenerate when the inflammatory process is stopped, the extracts of genus *Boswellia* and/or KBA may be an option in the treatment/prevention of autoimmune diabetes [62].

A dose of 200 mg/kg of *B. serrata* extract lowers glucose levels in the blood of rats with induced diabetes [63]. In preclinical studies, administration of doses from 250 up to 500 mg in patients with diabetes did not show a significant reduction of glucose levels in blood [64].

In people with genetic autoimmune diabetes, viruses or environmental factors may stimulate immunocompetent cells (macrophages, T lymphocytes) to secrete proinflammatory cytokines (IL-1, IL-2, IL-6, TNF- α , INF- γ). In this case, they are directed to the Langerhans cells of the pancreas, where they cause insulinitis by infiltration of macrophages and T lymphocytes. They release IL-1 and TNF- α which are responsible for β -cell death [62].

KBA inhibits the expression of proinflammatory cytokines from immune-competent cells and the infiltration of lymphocytes into the pancreatic islets, thus preventing insulinitis and β -cell death [62].

Essential oil of Indian frankincense

Methods for obtaining essential oil

Essential oils can be isolated from different parts of a plant by different methods. Which method will be applied depends on: the content of oil, the plant material and the economy of the procedure [65]. The nature of the components which are constituents of the essential oil, as well as the plant material in which the oil is located (root, bark, stem, leaf, flower, fruit and seed) is also important in choosing which isolation method to apply.

Conventional methods used to obtain biologically active compounds from plant raw materials are: water distillation, steam distillation, and water and steam distillation combined [66].

These conventional methods have numerous disadvantages, such as potential degradation of thermolabile compounds and long distillation time [67]. Supercritical fluid extraction is an alternative technique to conventional methods of isolating essential oils, with advantages such as lower operating temperatures, environmental friendliness and lower solvent consumption [68]. For the commercial extraction of aromatic compounds from plants, a temperature of 0-10 °C is most often used, and a 60-80 bar pressure. Extraction at low temperatures allows the separation of compounds, which may otherwise be lost due to evaporation or dissolution in water and/or transformed by conventional distillation.

Essential oil from *B. serrata* resin is obtained by steam distillation [69]. It is one of the oldest, but most common methods to obtain essential oils. It is used for raw materials with a relatively high content of essential oil and for essential oils whose components are stable at

operating temperatures [65].

Chemical composition and pharmacological activities

The essential oil of Indian frankincense shows a full spectrum of pharmacological activity, including anticancer, antimicrobial, psychopharmacological, antiulcer and antioxidant potential.

The GC/MS method has shown that the essential oil of Indian frankincense (*B. serrata*) contains monoterpenes, of which α -thujone is the most represented constituent. Other identified monoterpenes are: α -pinene, sabinene, δ -3-carene, *cis*-verbenol, *trans*-pinocarveol, borneol, myrcene, verbenone, limonene, tuja-2,4 (10)-diene and *p*-cymene, while copaene is the only sesquiterpene identified in oil [70, 71, 72]. Except in terpenoids, phenolic compounds and diterpene alcohol (seratol) are also constituents of essential oil [73]. The structures of the most common components isolated from the essential oil of frankincense are shown in Figure 4.

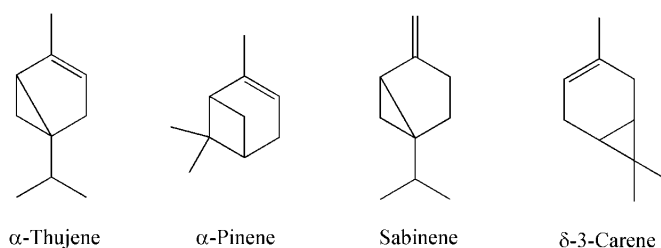


Figure 4. Chemical structural formulas of the most common components identified in the essential oil of Indian frankincense (*B. serrata*)

α -Thujone acts on GABA as an antagonist (opposite to the effects of alcohol) [74]. α - and β -pinene show different biological activities, and therefore have different applications and uses. There is a full range of pharmacological activities, including modulation of antibiotic resistance, anticoagulant, antitumor, antimicrobial, antimalarial, antioxidant, anti-inflammatory and analgesic effects [75].

Antibiotic Resistance Modulation

The ability of bacteria to gain resistance to antibiotics is one of the major problems in medicine. Approximately 25 000 patients die each year in Europe due to an infection with bacteria resistant to conventional antibiotics. For example *Campylobacter jejuni* causes gastroenteritis and shows resistance to different antibiotics. α -pinene has been used as a modulator of antibiotic resistance of *C. jejuni* [76].

The study showed that α -pinene modulates antibiotic resistance by reducing the MIC (minimum inhibitory concentration) of ciprofloxacin, erythromycin and triclosan up to 512 times [75].

Antitumor activity

A tumor is a disease in the growth and differentiation of cells that is characterized by abnormal cell prolifera-

tion. Among malignant tumors, lung tumor is the most common in the world causing the mortality of 1.38 million people each year [77]. α -pinene is a terpenoid with anticancer activity and is used for the treatment of ovarian cancer, hepatocellular carcinoma and N2a neuroblastoma [78, 79, 80]. α - and β -pinene have shown strong anticancer activity in synergism with paclitaxel (a drug used in breast cancer therapy) [81]. Essential oil obtained by hydrodistillation in which α - and β -pinene are the most abundant has shown anti-proliferative activity against breast cancer (MDAMB-231 and MCF-cell) [82].

Antimicrobial and antimalarial effects

In the study conducted by Bait et al. (2008) the results have shown that (+)- β -pinene is approximately 2–12 times more active compared to (+)- α -pinene against Gram-positive and Gram-negative bacteria, and also against yeast *Candida albicans* [83].

They are used as antibacterial agents due to their toxic effects on the membranes of the infective agents [84]. It is shown that they have an inhibitory effect on breast cancer and leukemia [85].

Also, it has been shown that (+)- α -pinene has 250 times higher antimalarial activity compared to (+)- β -pinene. When speaking of antioxidant activity, it has been confirmed that terpenes have stronger antioxidant activity than other compounds, such as vitamin C [86].

Antibacterial activity of essential oil

The essential oil of Indian incense was tested against Gram-positive and Gram-negative bacteria. It showed significant inhibitory activity against *Staphylococcus aureus*, *Escherichia coli* and *Proteus mirabilis* [70]. Basar noted that components responsible for antibacterial activity are incensol, vertikila-4 (20), 7,11-triene, AKBA, 3-oxo tirulic acid and α - and β -boswellic acid [87].

Abdoul-latifet et al. (2012), have proven the antibacterial activity of essential oils obtained from *B. sacra* and *B. papyrifera*. It is interesting that these essential oils show stronger antibacterial activity than tetracyclines [88].

Antifungal effects

Antifungal effects or potential antifungal effects were investigated by Camarda et al. (2007) and Sadhasivam et al. (2016). These studies have shown that essential oils obtained from different species such as *B. carterii*, *B. serrata*, *B. papyrifera* and *B. rivae* have antifungal activity against *Malassezia spp.*, *C. albicans* and *Trichophyton spp.* [89, 90]. Also, resin and essential oil of *B. sacra* could be used as food preservatives

Neuroprotective activities

Oxidative imbalance can cause neurodegenerative diseases, such as Alzheimer's or Parkinson's [91]. Lower production of free radicals is vital for good brain function and it reduces the development of neurodegenerative disorders. Porres-Martinez et al. used mouse pheochromocytoma cells (PC12) as a model and analyzed the ef-

fect of α -pinene on H₂O₂-induced oxidative stress. They concluded that α -pinene stops the intracellular production of free radicals [91].

Inhibitory effect on the growth of endocarditis disease

Infectious endocarditis is an inflammation of the inner layer of the heart wall, most often caused by bacteria, and less often by fungi. Microorganisms belonging to the genus of *Streptococcus* and *Staphylococcus*, *Haemophilus parainfluenzae*, *H. aphrophilus*, *H. paraphrophilus*, *H. influenzae*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella denitrificans* are the main microbes which cause inflammation of endocardium. In one study, the investigation was focused on slowing the development of endocarditis by using α - and β -pinene. *S. aureus*, *Staphylococcus epidermidis*, *Staphylococcus pneumoniae* and *Staphylococcus pyogenes* were used for the suggested screening. α - and β -pinene showed inhibitory effects against the mentioned bacteria. In addition, some strains have shown resistance to antibiotics (mainly gentamicin), while *S. aureus* was resistant to α - and β -pinene [75].

Anti-inflammatory and analgesic properties

Inflammation is an immune response that protects the body from infection [92]. The anti-inflammatory effect of α -pinene on peritoneal macrophages of male (C57BL/6) rats was tested in a study [92]. α -pinene reduces the production of IL-6 and TNF- α in macrophages of rats. Nitrite production was also reduced by α -pinene.

Branded formulations with resin isolate *B. serrata*

Various activities exhibited by isolates (essential oil, extracts) from *B. serrata* resin have led to the development of branded formulations in the cosmetics industry (perfumes, soaps, creams, lotions, detergents) giving products an oriental perfumed note and being used in the pharmaceutical industry most often in the form of capsules, tablets and creams mainly for the relief of anti-inflammatory problems, joint pain, analgesia of various etiologies, rheumatoid gout, osteoarthritis and sciatica. Table 2 lists the products that can be found on the market, as well as the companies that produce them, with indications and doses [93].

Table 2. Some of the branded formulations containing *B. serrata* available in the market [93]

Products	Company	Formulations	The content of an active compound	Indications and doses
Boswellin®	Sabinsa Corporation	Capsules, tablets	150-250 mg/capsules or tablets of boswellic acids	For pain treatment, orally two to three times a day
Shallaki®	Himalayan Drug Company,	Capsules	125 mg Boswellia serrata	Antiinflammatory and analgesic properties, useful in relieving joint pains, 1 capsule twice a day
Niltan®	Dr. Reddy's Laboratories Limited, Hyderabad	Cream	Combination of active herbal extracts (boswellin, arbutin, liquorice extract and coriander seed oil in a cream base)	Reduces the activity of the enzyme tyrosinase within the skin, thus diminishing the production of melanin, an external application
Rheumatic-X®	Sunrise Herbals, Varanasi (U.P., India)	Capsules	20 mg 'Shallaki' besides several ingredients	Rheumatoid gouty, osteoarthritis and sciatic pain, two capsules twice daily

Conclusion

Frankincense is very popular today in modern medicine due to its numerous biological effects. This fragrant resin is used for religious purposes, but also in aromatherapy and natural healing. As it is not possible to cultivate it, because it grows only in a certain habitat, incense is an exceptionally endangered species, but also highly valued for its biological potential.

Boswellic acids isolated from the resin of frankincense, and first of all AKBA, have a pronounced anti-inflammatory and anti-cancer effect. These effects are related to the inhibition of 5-LOX, leukocyte elastase, topoisomerase and C2 convertase. The essential oils of the genus *Boswellia* have a pleasant smell, contain different terpenes and have an antimicrobial effect on different types of microbes. Also, frankincense oil has antioxidant, anticancer, neuroprotective and anti-inflammatory potential. Based on the review of the pharmacological activity of active components from the resin of *B. serrata* frankincense, it can be concluded that this natural resource is very valuable and interesting in the field of science for further research, as a source of potential new medicinal agents.

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Abbreviations

ABA - acetyl- β -boswellic acid

AKBA - acetyl-11-keto- β -boswellic acid

BA - β -boswellic acid

BSE - *Boswellia serrata* extracts

COX-2 - cyclooxygenase-2

HLE - human leukocyte elastase

INF γ - interferon gamma

iNOS - inducible nitric oxide synthase

IL - interleukin

KBA - 11-keto- β -boswellic acid

5-LOX - 5-lipoxygenase

MIC - minimum inhibitory concentration

NAFLD - non-alcoholic fatty liver disease

NSAID - non-steroidal anti-inflammatory drugs

TNF α - tumor necrosis factor- α

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Izvod

IZOLATI IZ SMOLE *BOSWELLIA SERRATA*: HEMIJSKI SASTAV I FARMAKOLOŠKE AKTIVNOSTI

Natalija G. Tošić, Vesna D. Nikolić, Vojkan M. Miljković, Ljubiša B. Nikolić

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Tehnološki fakultet, Univerzitet u Nišu, Leskovac, Srbija

Tamjan je aromatična smola koja se dobija od različitih vrsta drveta roda *Boswellia* iz porodice *Burseraceae*. Najveći medicinski značaj ima *Boswellia serrata*, karakteristična za indijski potkontinent, čiji su farmakološki efekti dokazani u brojnim studijama. Cilj ovog rada je detaljan literaturni pregled hemijskog sastava i biološke aktivnosti izolata iz smole indijskog tamjana (*B. serrata*). *In vitro* studije i brojna klinička ispitivanja pokazala su obećavajući blagotvorni efekat u lečenju inflamatornih bolesti, poput reumatoidnog artritisa, ulceroznog kolitisa, inflamatorne bolesti creva (ileitis), Kronove bolesti i astme, kao i u smanjenju peritumoralnog edema. Smola dobijena od vrste *B. serrata* koja ima verski i medicinski značaj, danas se u velikoj meri koristi i u kozmetičkoj industriji zbog visokog sadržaja etarskog ulja

Cljučne reči: *Boswellia serrata*, tamjan, bosvelična kiselina, smola, etarsko ulje