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Frankincense – therapeutic properties

Kadzidłowiec – właściwości terapeutyczne

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Summary

Recently, increasing interest in natural dietary and therapeutic preparations used as dietary supplements has been observed. One of them is frankincense. This traditional medicine of the East is believed to have anti-inflammatory, expectorant, antiseptic, and even anxiolytic and anti-neurotic effects. The present study aims to verify the reported therapeutic properties of *Boswellia* resin and describe its chemical composition based on available scientific studies. The main component of frankincense is oil (60%). It contains mono- (13%) and diterpenes (40%) as well as ethyl acetate (21.4%), octyl acetate (13.4%) and methylanisole (7.6%). The highest biological activity among terpenes is characteristic of 11-keto-ß-acetyl-beta-boswellic acid, acetyl-11-keto-ß-boswellic acid and acetyl-α-boswellic acid. Contemporary studies have shown that resin indeed has an analgesic, tranquilising and anti-bacterial effects. From the point of view of therapeutic properties, extracts from *Boswellia serrata* and *Boswellia carterii* are reported to be particularly useful. They reduce inflammatory conditions in the course of rheumatism by inhibiting leukocyte elastase and degrading glycosaminoglycans. *Boswellia* preparations inhibit 5-lipoxygenase and prevent the release of leukotrienes, thus having an anti-inflammatory effect in ulcerative colitis, irritable bowel syndrome, bronchitis and sinusitis. Inhalation and consumption of *Boswellia* olibanum reduces the risk of asthma. In addition, boswellic acids have an antiproliferative effect on tumours. They inhibit proliferation of tumour cells of the leukaemia and glioblastoma subset. They have an anti-tumour effect since they inhibit topoisomerase I and II-alpha and stimulate programmed cell death (apoptosis).

Key words: **frankincense • chemical composition • therapeutic properties**

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Abbreviations: **5-LO** – 5-lipoxygenase; **AK**β**-BA** – acetyl-11-keto-β-boswellic acid; **A**β**BA** – acetyl-β-boswellic acid; **COX** – cyclooxygenase; **IFN**γ – interferon gamma; **IKK** – IκBα kinases; **IL(1-12)** – interleukins 1-12; **KBA** – 11-keto-β-boswellic acid; **K**β**-BA** – 11-keto-β-boswellic acid; **LPS** – lipopolysaccharides; **LTB$_4$** – leukotriene B$_4$; **MAPK** – mitogen-activated protein kinase; **MIC** – minimum inhibitory concentration; **NF-κB** – neutrophil factor κB; **NK cells** – natural killer cells; **NOSs** – nitric oxide synthases; **TH1** – T helper 1 cells; **TNF-**α – tumour necrosis factor α.

Introduction

From the early ages of history, plants and plant products have been the primary source of food, shelter and transport materials, clothing, fragrances, flavours, and ingredients of medicinal substances for humankind. They comprised plants harvested and, with time, cultivated mainly for food. Plants or plant products used as herbs and for therapeutic purposes were particularly valuable and were sourced from the natural environment in small amounts. Over time, they became the object of trade and a source of income for local communities [1,5,21,43,55,62]. Such plant materials include *Boswellia*. For at least 3000 years, resin of *Boswellia tree*, which is also known as frankincense or olibanum, had been an important trade material for the civilizations located in the Arabian Peninsula and North Africa. Olibanum is a natural oleo-gum resin obtained through incisions made in the trunks of trees of the genus *Boswellia* (Family Burseraceae). The genus *Boswellia* comprises 25 species. The species are widely distributed in India (*Boswellia serrata*), on the Arabian Peninsula (*Boswellia sacra*), in North Africa, Somalia (*Boswellia carterii* and *Boswellia frereana*), Ethiopia (*Boswellia papyrifera* and *Boswellia rivae*) and Eritrea (*Boswellia neglecta*) [1,8,12].

Currently, in the age of widespread flow of raw materials and goods, *Boswellia* is also available in the European market. Due to its therapeutic properties, the plant is of interest both to doctors and to nutritionists. Traditionally, the oleo-gum resin of some *Boswellia* species such as *Boswellia serrata* and *Boswellia carterii* has been used in many countries for the treatment of rheumatic and other inflammatory diseases, including Crohn's disease and ulcerative colitis [9,47], although there are reports of the negligible effectiveness of *B. serrata* in recurrent diseases [38]. Furthermore, the extracts and essential oils of frankincense have been used as antiseptic agents in a mouthwash as well as in the treatment of coughs and asthma [9]. Many studies have reported on the anticancer, anti-inflammatory, immunomodulatory, antimicrobial, antiviral and even antidiabetic activities of several *Boswellia* species [2,3,5,8,9,43,52,54,56,58,76,90].

Frankincense is also of interest to producers of animal origin foods looking for natural supplements that ensure high yielding production, at the same time maintaining the animals in good health condition and creating the possibility to obtain healthy food [60]. Therefore, frankincense was entered into the European Union Register of Feed Additives [28].

Characteristics of chemical composition

According to physiochemical research, oil of *Boswellia* resin contains 13.1% monoterpenes, 1% sesquiterpenes and 42.5% diterpenes. Other major components of the oil include duva-3,9,13-trien-1,5alpha-diol-1-acetate (21.4%), octyl acetate (13.4%), o-methyl anisole (7.6%), naphthalene decahydro-1,1,4a-trimethyl-6-methylene-5-(3-methyl-2-pentenyl) (5.7%), thunbergol (4.1%), phenanthrene-7-ethenyl-1,2,3,4,4a,5,6,7,8,9,10,10a-dodecahydro-1,1,4a,7-tetramet hyl (4.1%), alpha-pinene (3.1%), sclarene (2.9%), 9-cis-retinal (2.8%), octyl formate (1.4%), verticiol (1.2%) decyl acetate (1.2%) and n-octanol (1.1%) [11,12,18,51,61,62,69,86,90].

Essential oil of *Boswellia carterii*

The essential oil of *Boswellia carterii* has been one of the intensively studied oils of olibanum. With its 60% predominance in the oil, octyl acetate was found to be the major constituent of the oil resin. The hydrodistillate of *B. carterii* was a pale yellow oil. Its major constituents were identified as α-thujene (1.7%), α-pinene (10.9%), camphene (1.0%), sabinene (0.7%), β-pinene (0.7%), myrcene (0.5%), hexyl acetate (0.3%), p-cymene (1.4%), Z-β-ocimene (0.4%), E-β-ocimene (1.7%), limonene (1.5%), 1,8-cineole (1.2%), 1-octanol (11.9%), linalool (2.1%), α-pinene epoxide (0.5%), *trans* verbenol (0.4%), terpinene-4-ol (0.4%), octyl acetate (39.3%), bornylacetate (2.2%), geranylacetate (0.4%), E-nerolidol (0.2%), cembrene A(2.1%), cembrene C (0.1%), verticilla-4(20),7,11-triene (6.0%), incensole (1.0%) and incensole acetate (2.3%). The n-hexane extract of *Boswellia carterii* was also found to contain diterpenoid constituents as well as octyl acetate, but lower amounts of monoterpenoid constituents [10,11,86] (fig. 1).

Essential oil of *Boswellia serrata*

The major component of the essential oil of *Boswellia serrata* was α-pinene, representing approximately 45% of the oil (table 1). The hydrodistillate of *B. serrata* is a colourless oil. Investigations have indicated that the oil consists of α-thujene (12%), α-pinene (8%), sabinene (2.2%), β-pinene (0.7%), myrcene (3.8%), α-phellandrene (1%), p-cymene (1%), limonene (1.9%), linalool (0.9%), perillene (0.5%), methylchavicol (11.6%), methyleugenol (2.1%), germacrene D (2.0%), kessane (0.9%), cembrene A (0.5%) and cembrenol (1.9%) as the major constituents (fig. 2). In addition to these, a monoterpene 5,5-dimethyl-1-vinyl-bicyclo- hexane (2%) and two diterpenoid components, m-camphorene (0.7%) and p-camphorene (0.3%), were

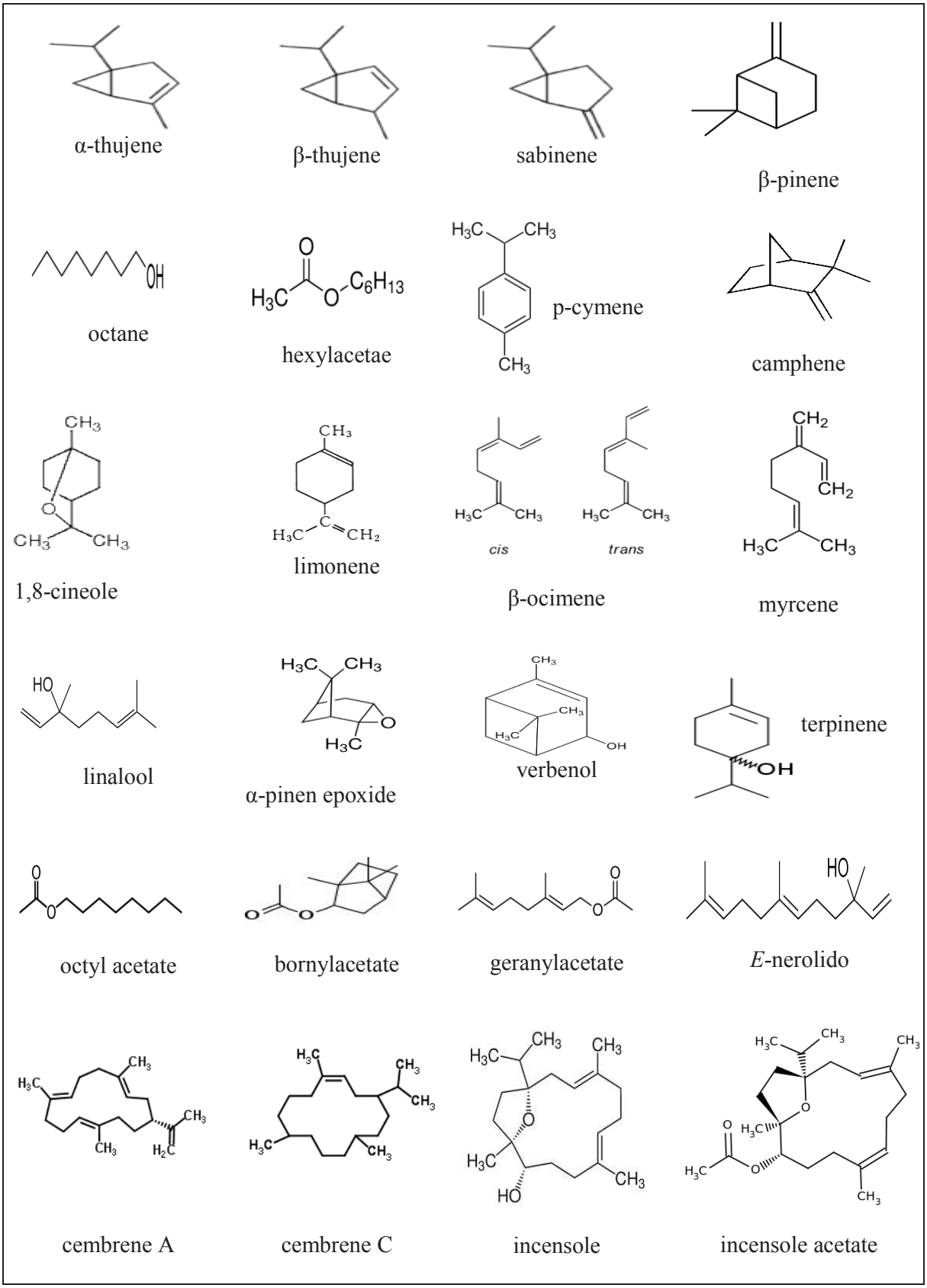

Fig. 1. The chemical components of the essential oil of *Boswellia carterii* [5,10,13,90]

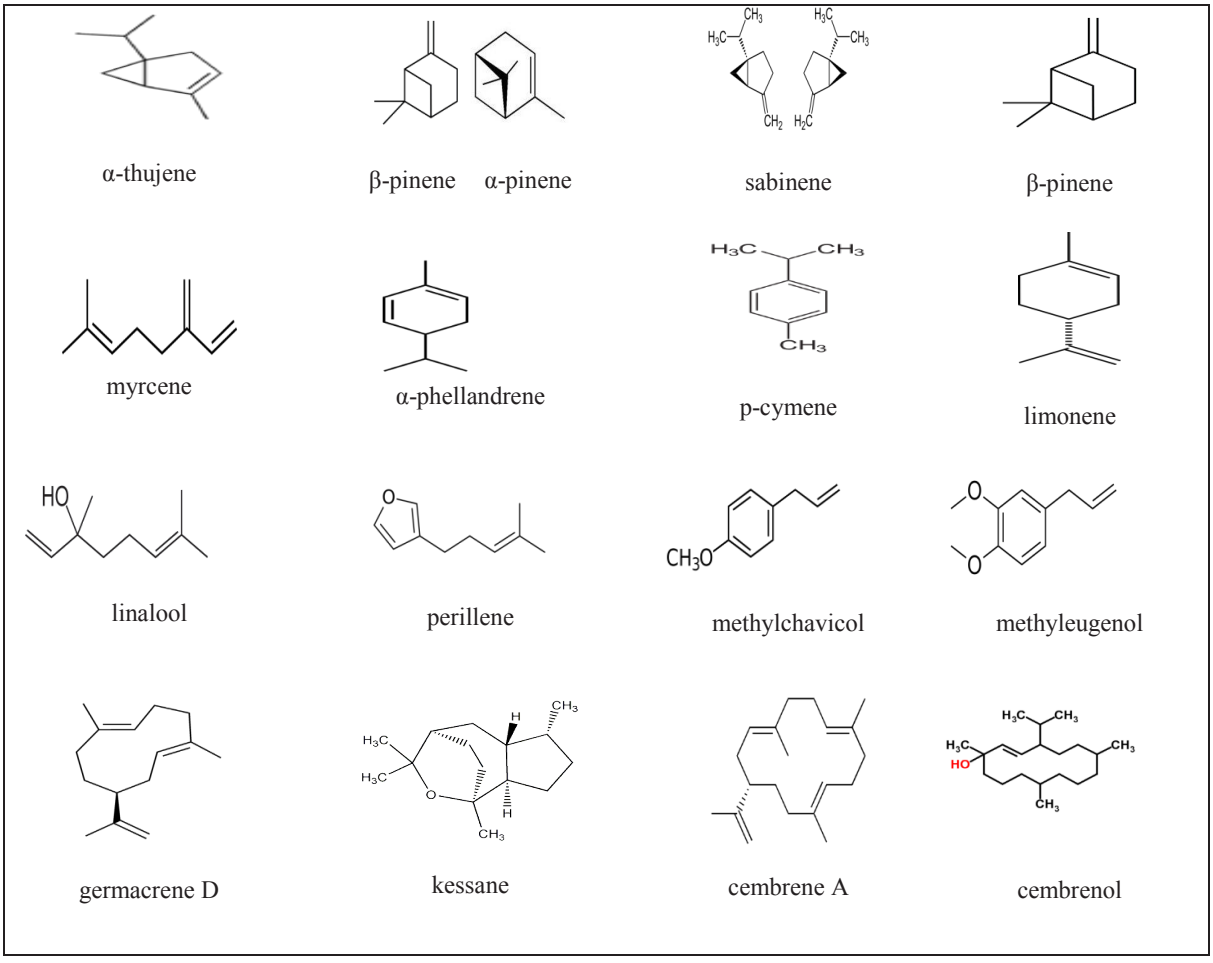

Fig. 2. The chemical components of the essential oil of *Boswellia serrata* [5,10,13,90]

isolated and identified from the essential oil of *B. serrata* [10,51,84].

The resinous part of *B. 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 the inhibition of pro-inflammatory enzymes (fig. 3). 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. The main constituents in *B. carterii* and *B. sacra* are α-pinene, limonene and β-caryophyllene. α-Thujene (with a value of 11.7%) is the dominant volatile in a *B. serrata* extract [35,77].

Chemical composition of *Boswellia* frankincense

Boswellia resin contains about 5-9% essential oil, 65-85% alcohol-soluble resin, and the remaining 21-22% is water-soluble gum (polysaccharidic fraction and polymeric substances). Four different types of proteoglycans and glycoproteins have been identified in frankincense products. The main components (32-56%) of the water-soluble polymeric substances from the resins of *B. carterii* and *B. serrata* are classical arabinogalactan proteins. These proteoglycans are mainly composed of D-galactose units (about 60 mol-%) in the core chains, which are highly branched via positions 3 and 6. In the side chains, there are uronic acids, glucuronic acid (9 mol-%) and terminal 4-O-methyl-glucuronic acid (13-26 mol-%), as well as arabinose (2-14 mol-%) [11,37].

In the polymer group, there are high contents of fructose, mannose and glucosamine, indicating the occurrence of glycoproteins. The carbohydrate part of neutral proteoglycans from the first group consists mainly of L-arabinose (ca. 90 mol-%) and D-galactose (8 mol-%). Arabinose units exist as linear 1,2 and in smaller amounts 1,3 chains with a high content of terminal arabinose units. The protein part is dominated by the amino acids hydroxyproline (about 50 mol-%) and serine (about 20 mol-%), indicating that these proteoglycans are extension structures. The main difference between the gum from *B. carterii* and *B. serrata* is the higher content of proteins (22%) in the gum from *B. serrata* than that from *B. carterii* (6%) [24].

Chevrier et al. [27] and Thorne [20] reported that *B. carterii* and *B. serrata*, apart from sugars and oil, contain volatile

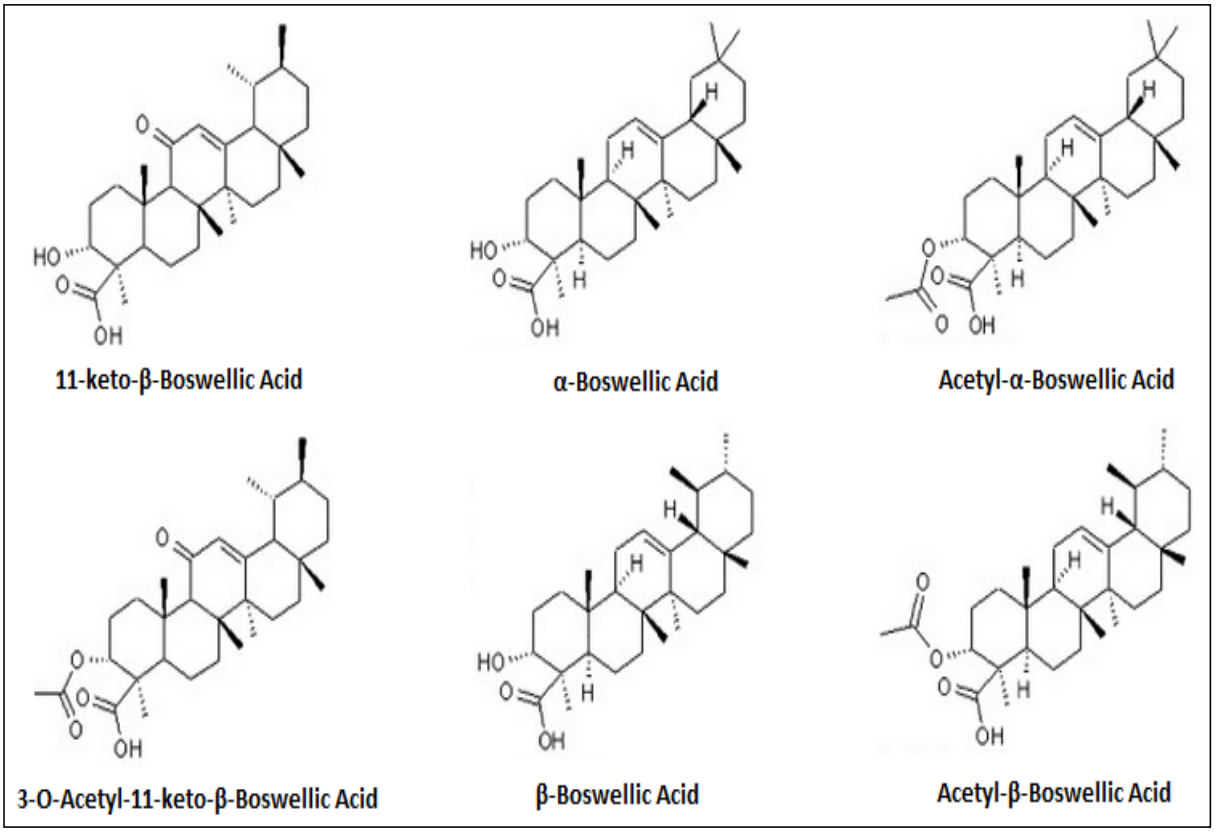

Fig. 3. Major pentacyclic triterpenic acids in *Boswellia* [11,12,69,85,90]

oils and terpenoids, as well as aliphatic octyl acetate responsible for the strong odour when burned; they also contain many other active compounds (incensole, incensole acetate, pentacyclic triterpene boswellic acids, α- and β-boswellic acid, 11-keto-β-boswellic acid, acetyl-11-keto-β boswellic acid, acetyl-11dien-β boswellic acid, acetyl-α-boswellic acid and acetyl-β-boswellic acid).

Incensole and incensole acetate are specific biomarkers for *B. papyrifera*; *B. carterii* and *B. sacra* exhibit ß-caryophyllene oxide as a significant marker compound. *B. serrata* shows neither incensole acetate nor ß-caryophyllene oxide spots, but can be identified by a strong serratol and a sharp 3-oxo-8,24-dien-tirucalli acid spot [59,66]. The resin of *B. carterii* contains incensole acetate (32.0%), octanol acetate (25.1%), incensole (17.8%) and phyllocladene (7.7%) [21]. The percentage of the main constituents in the oil obtained by higher resolution was quite different. It contained larger amounts of octanol acetate (45.2%) and phyllocladene (13.2%) and lower amounts of incesole (6.1%) and incensole acetate (13.0%). Many researchers have reported the presence of incensole, incensyl acetate and verticilla-4,7,11-triene. Cembrene, cembrene A and cembrene C were found to be characteristic for *B. carterii*. [15,48,50,90]. On the other hand, the presence of m- and p-camphorene, cembrene A and cembrenol was recognized as a diagnostic marker. The 3-oxo-tirucallic acid, an additional tetracyclic triterpene isolated from *B. serrata* resin, as well as 3-acetoxy-tirucallic acid and 3-hydroxy-tirucallic acid, was biologically active [18].

Moreover Mikaeil et al. [52] observed the presence of limonene (22.4%) and a high proportion of esters, e.g. duva-3,9,13-trien-1,5a-diol-1-acetate (21.4%), as predominant compounds in *B. carterii*.

Buchele et al. [23] reported having identified compounds of *B. serrata* and the *B. carterii*. The results showed a significant difference in the ratio of AKβ-BA (4acetyl-11-keto-β-boswellic acid) to Kβ-BA (11-keto-β-boswellic acid). In these resins, AKβ-BA was found to be the predominant compound in *B. carterii*, while twice as much Kβ-BA was found in *B. serrata*. The ratio of these compounds (4:3) is approximately 0.7 and 4.7 in *B. serrata* and *B. carterii*, respectively. Furthermore, the results indicated that the total amount of pentacyclic triterpenic acids present was approximately 25% lower in *B. serrata* than in *B. carterii*. In this context, Siddiqui [77] found that the resinous part of *B. 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.

Therapeutic activity

Anti-bacterial activity

The acid fractions of *B. carterii* and *B. serrata* are characterized by high antibacterial activity. Basar [12] discovered antibacterial activity against *Bacillus* in *B. carterii* oil. The main active substances were verticilla-4(20),7,11-triene and incensole. Also in *B. carterii*, antibacterial activity was exhibited by acetyl-keto-boswellic acid (AKBA), α- and β-BA and 3-oxo-tirucallic acid. In *B. serrata*, the activity of these compounds was found to be stronger.

The aqueous extract of *B. serrata* showed a large zone of inhibition against *P. vulgaris*. It displayed excellent antibacterial activity against *P. aeruginosa* and *P. vulgaris* with a minimal inhibitory concentration (MIC) value of 12.5 µg/µl [22,69]. A petroleum ether extract of *B. serrata* plant displayed excellent antibacterial activity against *P. aeruginosa* with a MIC value of 12.5 µg/µl. AKβ-BA isolated from *B. carterii* was found to be an active compound with a MIC range of 2-8 µg/ml against all Gram-positive bacterial pathogens tested. It exhibited a concentration-dependent bactericidal effect against *Staphylococcus aureus* [70]. An ether extract of *B. serrata* showed a large zone of inhibition against the Gram-negative organism *P. aeruginosa*, a methanol extract of *B. serrata* showed a large zone of inhibition against *P. vulgaris*, and an acetone extract of *B. serrata* showed a large zone of inhibition against *P. aeruginosa* [23]. The acetone extract of the *B. serrata* plant displayed excellent antibacterial activity against *E. coli* and *K. pneumoniae* with a MIC value of 12.5 µg/µl [71]. The methanol extract of the *B. serrata* plant displayed good antibacterial activity against *E. coli*, *P. aeruginosa* and *P. vulgaris* with a MIC value of 25 µg/µl.

The essential oil from the bark of *B. serrata* was tested against Gram-positive and Gram-negative bacteria [41,65,73,84]. It exhibited significant inhibitory activity against *S. aureus*, *E. coli* and *Proteus mirabilis*. Camarda et al. [24] investigated the antimicrobial efficacy of *B. carterii* against *E. coli* and *Pseudomonas aeruginosa.* Inhibitory activity was found against all pathogens, with the highest sensitivity noted for *P. aeruginosa* at concentrations as low as 6.6 µg/mL. Conversely, the essential oil of *B. carterii* was investigated for inhibitory activity against a methicillin-resistant *Staphylococcus aureus* (MRSA) strain using a disc diffusion assay and found to have no inhibitory activity. The different fractions of essential oils of *B. carterii*, *B. neglecta*, *B. sacra*, *B. thurifera* and *B. frereana* showed moderate to poor activity against a reference *S. aureus* strain. The oleo-gum resin of *B. serrata* was extracted with methanol and its antimicrobial activities were evaluated using two Gram-positive organisms (*Bacillus subtilis* and *Staphylococcus aureus*) and two Gram-negative organisms (*Salmonella typhi* and *Escherichia coli*); the extract exhibited significant antimicrobial activities [71,76]. Research on an alcohol extract of *B. carterii* was also conducted by Salman [75]. The alcoholic extract from *B. carterii* was evaluated by testing its extract against four types of bacterial growth; two of them were the Gram-positive bacteria *Staphylococcus aureus* (24 isolates) and *Streptococcus pyogenes* (18 isolates), and the other were the Gram-negative bacteria *E. coli* (35 isolates) and *Salmonella.* spp. (20 isolates). Five extract concentrations were used (25, 50, 75, 100 and 200 mg/ml). The extract showed antibacterial activity against all types of bacteria, and the zones of inhibition increased directly with the increasing concentration of the extract.

The anti-bacterial resin properties may be attributed to the presence of phenolic acid in boswellic acid. Phenolic compounds in organic acids improve the efficiency of protein and energy by reducing microbial competition with the host for nutrients and endogenous nitrogen losses, by lowering the incidence of subclinical infections and secretion of immune mediators, and by reducing production of ammonia [5,65]. Alsaba et al. [4] reported antibacterial activities of boswellic acids from *B. serrata* tested *in vitro* on a clinically significant panel of oral bacteria. Acetyl-keto-boswellic acid (AKBA) was the most active of the four boswellic acids against all bacterial pathogens. AKBA exhibited a MIC ranging from 2 to 4 µg/ml against all the tested strains except against *F. nucleatum*, showing a MIC > 128 µg/ml, whereas KBA and BA exhibited moderate anti-Gram-positive activity (MIC ≈ 8-64 µg/ml). All the compounds showed antibacterial activity, but AKBA was found to be the most active boswellic acid compound against Gram-positive bacterial pathogens.

Anti-fungal properties

The reference literature also reports that *Boswellia* resin has an antifungal effect. Camarda et al. [24] and Mothana et al. [56] reported that the essential oils from *B. carterii*, *B. papyrifera*, *B. serrata* and *B. rivae* oleo-gum resins exhibited high activity against fungal strains. The minimum

Table 1. The boswellic acids of *Boswellia serrata* [12]

Name of the acid	Molecular formula	[M+]	[M+] of TMS derivative
β-Boswellic acid (β-A)	C30H4803	456	600
3-*O*-Acetyl-β-boswellic acid (ABA)	C32H5004	498	570
3-*O*-Acetyl-11-keto-β-boswellic acid (KBA)	C32H4805	512	584
11-Keto-β-boswellic acid (KBA)	C30H4604	470	614
α-Boswellic acid	C30H4803	456	600

inhibitory concentration values were as low as 6.2 µg/ml. The essential oils of four *Boswellia* species exhibited significant antifungal activity against both *Candida albicans* and *Candida tropicalis*. The authors discovered that the limonene component present in the essential oils of *Boswellia* was responsible for the antifungal activity.

The essential oil of *B. carterii* exhibited significant inhibition of growth and aflatoxin production by a food-borne toxigenic strain of *Aspergillus flavus* at 1.75 Ml/ml and 1.25 Ml/ml, respectively. It exhibited a broad fungitoxic spectrum against 12 food-borne moulds and showed strong antioxidant activity, with an IC_{50} value and % inhibition of linoleic acid peroxidation of 0.64 ml/ml and 51.68%, respectively [14].

Anti-inflammatory properties

Pro-inflammatory cytokines such as TNFα, IL-1β and IL-6 play an important role in the inflammatory response. The inflammatory cytokines play an important role in the modulation of acute and chronic inflammation [47,76]. Thus, TNF-α- and IL-1β activate inflammatory cells and induce production of other inflammatory mediators, which in turn modulate important cellular events including gene expression, DNA damage and cellular proliferation contributing to various inflammatory disorders. Therefore, cellular manipulation of the production of TNF-α- and IL-1β is important for regulating the inflammatory response [44]. Eicosanoids are also potent lipid mediators of inflammation. An important role is played by their compounds: specifically, leukotrienes, prostaglandins and lipoxin. They are derived from phospholipase-released arachidonic acid through subsequent metabolism by (COX)-1/2 or LOX and are involved in a variety of homeostatic biological functions and inflammation. With the liberation of arachidonic acid in the cell, several enzymatic reactions take place involving different types of enzymes, such as 12-LOX, 5-LOX, 15-LOX and COX, and each reaction leads to the production of a different type of an inflammation mediator [63].

The resinous part of *B. serrata* contains monoterpenes, diterpenes, triterpenes, tetracyclic triterpenic acids and four major pentacyclic triterpenic acids, namely fl-boswellic acid, acetyl-fl-boswellic acid, 11- keto-fl-boswellic acid and acetyl-11-keto-fl-boswellic acid [77,79,85]. Among these four boswellic acids, acetyl-11-keto-fl-boswellic acid has been determined to be the most potent inhibitor of 5-lipoxygenase, an enzyme that is key to the biosynthesis of leukotrienes from arachidonic acid in the cellular inflammatory cascade. The boswellic acid from *B. carterii* inhibited the production of inflammatory mediators and reduced the production of leukotrienes through its inhibitory action on lipoxygenase [9,64,76]. In this context, Bishnoi et al. [16] explained that boswellic acid was found to be a specific, non-reducing type inhibitor of 5-LOX activity acting either by interacting directly with 5-LOX or by blocking its translocation. The suppression of leukotriene synthesis via inhibition of 5-LOX is considered the main mechanism underlying the anti-inflammatory effect of boswellic acid. Clinical tests have confirmed that the anti-inflammatory activities of the triterpenoid resinous metabolites are largely ascribed to the inhibition of 5-lipoxygenase (5-LOX), nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) and nuclear factor- κB (NF-κB) activities. COX-2 and 5-LOX, two enzymes involved in the oxygenation of arachidonic acid, are upregulated in the central nervous system during aging and are associated with various aging-related brain pathologies [7,16]. 5-LO is an enzyme which catalyses the transformation of arachidonic acid to LTA4, which is in turn converted into leukotriene B4 (LTB4) or leukotriene C4 (LTC4) [87]. More detailed investigations showed boswellic acids as novel non-redox inhibitors, which bind to a selective site for pentacyclic triterpenes on 5-LO [74]. AKBA was the most efficient boswellic acid tested, with IC_{50} values of 1.5-50 µM, depending on the experimental settings (cell type, stimulus, animal or human cells) [3,74]. Higher concentrations of AKBA were needed to inhibit isolated 5-LO than 5-LO in intact cells. This indicates that the efficient inhibition in intact cells may be dependent on additional cellular mechanisms. When used in lower concentrations, a *B. serrata* extract elevated 5-LO activity [74]. AKBA or KBA (<30 µM) are incubated with arachidonic acid in polymorphonuclear leukocytes (PMNL). AKBA was identified as a direct inhibitor of cyclooxygenase-1 (COX-1), while COX-2 was only slightly inhibited by boswellic acids [68,78]. Boswellic acids are responsible for inhibiting 5-lipoxygenase in a non-redox and non-competitive manner, leading to inhibition of leukotriene biosynthesis in neutrophilic granulocytes. Furthermore, they can inhibit elastase in leukocytes, induce apoptosis, and suppress topoisomerases of leukoma and glioma cell lines [5].

Antioxidant activity

The literature mentions antioxidative properties of *Boswellia* resin. Pharmacokinetic tests of gum resin of *B. carterii*, *B. frereana*, *B. sacra* and *B. serrata* have shown that they are moderate to potent inhibitors of CYP enzymes, with equal potency for inhibiting the major drug metabolizing enzymes 1A/2C8/2C9/2C19/2D6 and 3A4 [31,35,88]. P450 (CYP) is a large and diverse group of enzymes that catalyse the oxidation of organic substances. The substrates of CYP enzymes include metabolic intermediates such as lipids and steroidal hormones [46,51]. On the other hand, Hartman et al. [36] mentioned other antioxidants. They reported the presence of limonene (22.4%) and a high proportion of esters, e.g. duva-3,9,13-trien-1,5a-diol-1-acetate (21.4%), as predominant compounds in antioxidant activity.

Zaki et al. [89] observed a mild cardioprotective effect and weak antioxidant activity in investigations of the cardioprotective and antioxidant activities of olibanum from a *Boswellia* species. *B. carterii* was the subject of this study. Cardioprotective activity was evaluated using a model of myocardial infarction induced by isoprenaline, while

antioxidant activity was tested with nitric oxide scavenging and azino-bis-3-ethyl benzothiazoline-6-sulfonic acid (ABTS) assays.

Immunomodulators

The basic mechanisms of the immunostimulatory, anti-tumour, bactericidal and other therapeutic effects of botanical polysaccharides are thought to occur via macrophage stimulation and modulation of the complement system; furthermore, modulation of these systems can significantly impact both humoral and cellular immune responses [6,13,36,57].

Extracts from the gum resin of *B. serrata* and *B. papyrifera* have an effect on the immune system. The immunomodulatory bioassay-guided fractionation of the oleo-gum resin of frankincense (*B. carterii*) resulted in isolation and identification of 9 compounds; palmitic acid and eight triterpenoids belonging to lupane, ursane, oleanane and tirucallane skeleta were isolated from the resin [8,17]. These triterpenoids are lupeol, beta-boswellic acid, 11-keto-beta-boswellic acid, acetyl beta-boswellic acid, acetyl 11-keto-beta-boswellic acid, acetyl-alpha-boswellic acid, 3-oxo-tirucallic acid and 3-hydroxy-tirucallic acid. Among the various boswellic acids, 11-keto-β-boswellic acid (KBA) and acetyl-11-keto-β-boswellic acid have been observed to be active [7]. In the humoral defence system, a mixture of boswellic acids at higher doses reduced primary antibody titres; on the other hand, lower doses enhanced secondary antibody titres following treatment with sheep erythrocytes. In the cellular defence, boswellic acids appear to increase lymphocyte proliferation, whereas higher concentrations are even inhibitory. Moreover, boswellic acids increase phagocytosis of macrophages. They affect the cellular defence system by interaction with production/release of cytokines. Thus, boswellic acids inhibit activation of NFκB, which is a product of neutrophil granulocytes. Consequently, downregulation of TNF-α and a decrease in IL-1, IL-2, IL-4, IL-6 and IFN-γ, which are proinflammatory cytokines, by boswellic extract and boswellic acids have been reported. A further target of the extract and boswellic acids in the immune system is the complement system, where inhibition of C3-convertase has been reported.

The effect of an extract from *B. carterii* on the production of TH-2 cytokines by murine splenocytes was studied by Chevrier et al. [27]. In these *in vitro* experiments, application of the resin extract, using ethanol as a solvent, showed significant cellular toxicity not seen with ethanol alone. Interestingly, the use of an extract with sesame oil as a solvent resulted in dose-dependent inhibition of TH-1 (IL-2 and IFN-gamma) and dose-dependent potentiation of TH-2 (IL-4 and IL-10.(A crude methanolic extract from *B. serrata* and 12-ursine-2-diketone, a pure compound of BS, inhibited TNF-α-, IL-1 β and IL-6 in cultured peripheral blood mononuclear cells [33]. Observations of TH1/TH2 cytokines revealed marked downregulation of IFN-α- and IL-12, whereas IL-4 and IL-10 were upregulated after treatment with a crude extract and the pure compound 12-ursene-2-diketone, indicating that both are capable of carrying out anti-inflammatory activity at sites where chronic inflammation is present by switching off the pro-inflammatory cytokines. On the other hand, in a study by Khajuria et al. [42], it was demonstrated that oral administration of 1–10 mg/kg of a polymeric fraction (BOS 2000) from *B. serrata* increased levels of IL-4, IFN-α and TNF-α- in the serum. Taking *in vitro* results together, it appears possible that if transferable to the *in vivo* situation, *Boswellia* extracts may decrease the cellular activity of the immune system through inhibition of activation, proliferation and differentiation of B- and T-lymphocytes (IL-1, IL-2, IL-4, IL-6), tissue destruction (IL-1), action of NK cells (IL-12), antibody production (IL-6) and fever (IL-1, IL-6) [47].

Moussaieff et al. [59] found that an incensole acetate extract from *B. carterii* inhibited the formation of interleukin (IL)-1β. IL-6 from the family of cytokines is secreted by T cells and macrophages to stimulate an immune response. It can be produced by many other cell types such as CD4+ lymphocytes, NK cells and neurons, as well as prostaglandins. IL-6 has been proposed to affect glucose homeostasis and metabolism directly and indirectly by action on skeletal muscle cells, adipocytes, hepatocytes, pancreatic β-cells and neuroendocrine cells. Interleukin 6 (IL-6), which acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine, tumour necrosis factor-α (TNF-α) and interleukin-1 β (IL-1β) are involved in the establishment of inflammatory lesions in periodontitis. High production of these cytokines may be associated with the severity of periodontitis [80].

Syrovets et al. [81] reported that acetyl-α–boswellic acid and AKBA inhibited the generation of TNF-α in concentrations between 1 and 10 μM in lipopolysaccharide-stimulated human monocytes. AKBA was found to be the most active compound. The effect was mediated by direct inhibitory action on I_K B-α-kinases (IKK)-conveyed inhibition of NF-κB and subsequent downregulation of TNF-α-expression in human monocytes. In human monocytes, concentration-dependent inhibition of TNF-α and IL-1 β production in a concentration range of 5–20 μM was observed.

Anticancer activity

Boswellic acid and its structurally related derivatives (i.e., constituents of the methanol extract derived from *B. serrata*) have anticarcinogenic, antitumour and antihyperlipidaemic activities [26,39,45,49]. Many authors [63,67,82] have reported that several trepertinoid acids isolated from *B. serrata* and *B. carterii* were characterized by an anti-proliferative effect of cytotoxic and cytostatic agents.

The cytotoxic action of AKBA on meningioma cells may be mediated, at least in part, by inhibition of the ERK (extracellular signal regulated kinases) signal transduction pathway [63,64]. ERK is a chain of proteins in the cell that

communicates a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell. A *Boswellia* extract from *B. serrata* with the defined boswellic acid content in acetyl-11-keto-beta-boswellic acid was more effective at inhibiting cancer cell growth than pure 3-O-acetyl-11-keto-beta-boswellic acid [39].

In vitro evaluations of the anti-cancer effects of boswellic acid acetate (BC-4), a compound isolated from a *B. carterii* extract, can induce differentiation and apoptosis of leukaemia cells [91]. BC-4 induced monocytic differentiation of myeloid leukaemia HL-60, U937 and ML-1 cells at a dose under 12.5 μg/ml. BC-4 failed to induce differentiation of erythroid leukaemia DS-19 and K562 cells. In contrast to its selective differentiation effect, BC-4 strongly inhibited growth of all cell lines tested. Morphologic and DNA fragmentation analysis showed that BC-4 induced cell apoptosis. The dual apoptotic and differentiation effects of BC-4 suggest that it may be a powerful agent in the treatment of leukaemia.

B. carterii may lead to activation of genes responsible for cell cycle arrest, growth inhibition and apoptosis [26]. These properties can be used in alternative treatment of bladder cancer. Frank et al. [32] emphasized the potential of the *B. carterii* extract to destroy cancer cells at the stage of differentiation of healthy and cancer cells.

Anti-arthritic activity

Rheumatoid arthritis is a disease affecting 2–3% of the population in the USA and 0.5-2% in Europe [30]. Conventional medicine includes treatment with steroids, nonsteroidal anti-inflammatory drugs (NSAIDs) and such biological agents as tumour necrosis factor alpha (TNF-α-) and interleukin-1 beta (IL-1β) antagonists. Fan et al. [29] reported that an acetone extract of *Boswellia carterii* gum resin decreased arthritic scores, reduced paw oedema and significantly suppressed local tissue TNF-α- and IL-1β in rats. Kimmatkara et al. [44] carried out similar studies involving a group of 30 patients with osteoarthritis of the knee. All patients receiving *Boswellia* treatment reported a decrease in knee pain, increased knee flexion and increased walking distance. The frequency of swelling in the knee joint was decreased. The *Boswellia* extract is recommended in patients with osteoarthritis of the knee with possible therapeutic use in other arthritis cases [44].

Juarranz et al. [40] observed a relationship between inflammation and bone homeostasis in rheumatoid arthritis attributed to the effects of cytokines such as TNF-α, IL-1β, IFN-α- and IL-6, which are abundantly expressed in patients with retinoid acid (RA) and in the arthritic joints of rats with collagen-induced arthritis, while IL-4 and IL-10 have potent anti-inflammatory effects and suppress cartilage and bone pathology in RA. In this context, the results obtained by Borrelli et al. [19] confirmed that, at a dose of 200 mg/kg, *B. serrata* extracts shift the balance of cytokines towards a bone-protecting pattern, which acts to both reduce the levels of TNF-α-, IL-1β and IFN-α and raise the levels of IL-10. Boswellic acids are considered responsible for anti-inflammatory activity of the plant [83]. In addition to the anti-inflammatory effect, the extract of *Boswellia* species in particular showed considerable radical scavenging activity. Probably, the two effects are related. The results are in agreement with previous studies showing that *Boswellia* inhibits TH1 cytokines and promotes production of TH2 in DBA/2 splenocytes [26]. Also Cuzzocrea et al. [25] stated that NF-kB plays a central role in the regulation of many genes that induce TNF-α, IL-1β, IL-6, iNOS and COX-2, which are responsible for the generation of mediators or proteins in inflammation. It was demonstrated that these triterpene acids were able to block inflammatory reactions in both acute and chronic inflammation models [6,54,83].

Stimulation of the gastrointestinal tract

The presence of *B. carterii* in the digestive system is considered as a stimulant, gas repellent and a catalyst for the appetite; it was also found to increase the flow of digestive juices, thus leading to improvement in digestion and absorption. It is possible that, since the organic acids in boswellic acid stimulate the secretion of pancreatic enzymes, they could improve protein and energy digestibility by reducing microbial competition with the host for nutrients and endogenous nitrogen losses, by lowering the incidence of subclinical infections and secretion of immune mediators, and by reducing production of ammonia and other growth-depressing microbial metabolites. These include reduction in digesta pH, increased pancreatic secretion and trophic effects on the gastrointestinal mucosa [72]. Miller et al. [53] stated that *Boswellia* species are among the most important medicinal plants used for relieving fever and pain as well as soothing an upset stomach.

In the clinical study by Gupta et al. [34] with patients suffering from chronic colitis, *B. serrata* resin (300 mg 3 times daily for 6 weeks) was examined and compared with sulfasalazine (1 g 3 times daily for 6 weeks), which served as a control. The patients were then tested for stool properties and histopathology, as well as scanning electron microscopy and determination of haemoglobin, serum iron, calcium, phosphorus, proteins, total leucocytes and eosinophils. Out of the patients treated with *Boswellia* gum resin, 90% showed an improvement in one or more of the parameters. In the control group, 60% of the patients achieved similar results. Out of the patients treated with *Boswellia* gum resin, 70% went into remission while in the case of sulfasalazine the remission ratio was 40%.

Conclusion

Boswellic acids have the structure of pentacyclic triterpenes. In the traditional medicine of the Middle and Far East, they are used in the treatment of inflammatory conditions of joints and bones, spinal cord and respiratory disorders. They are used as expectorant, antiseptic, anxiolytic and anti-neurotic drugs. In Ayurvedic medicine, they are an important anti-rheumatic drug.

Contemporary studies have shown that olibanum indeed has analgesic, tranquilising, and anti-bacterial effects. Alcohol extracts from olibanum inhibit the growth of fungi and bacteria. From the point of view of therapeutic properties, extracts from *Boswellia serrata* and *Boswellia carteri* are reported to be particularly useful. They reduce inflammatory conditions in the course of rheumatism by inhibiting leukocyte elastase and degrading glycosaminoglycans (in joints with inflammatory lesions). *Boswellia* preparations inhibit 5-lipoxygenase and prevent the release of leukotrienes, thus having an anti-inflammatory effect in ulcerative colitis, irritable bowel syndrome, bronchitis, and sinusitis. Inhalation and consumption of *Boswellia* gum resin reduces the risk of asthma. In addition, boswellic acids (in particular *Boswellia carteri)* have an antiproliferative effect on tumours. They inhibit proliferation of tumour cells of the leukaemia and glioblastoma subset. The components of *Boswellia* have an anti-tumour effect since they inhibit topoisomerase I and II-alpha and stimulate programmed cell death (apoptosis).

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