

***Boswellia Serrata*, A Potential Antiinflammatory Agent: An Overview**

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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

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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, Guguladhup
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 (macrocylic 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 (LTB₄), 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, where as boswellic acids seem to be specific inhibitor of 5-LO^[39]. 5-LO generates inflammatory leukotrienes, which cause

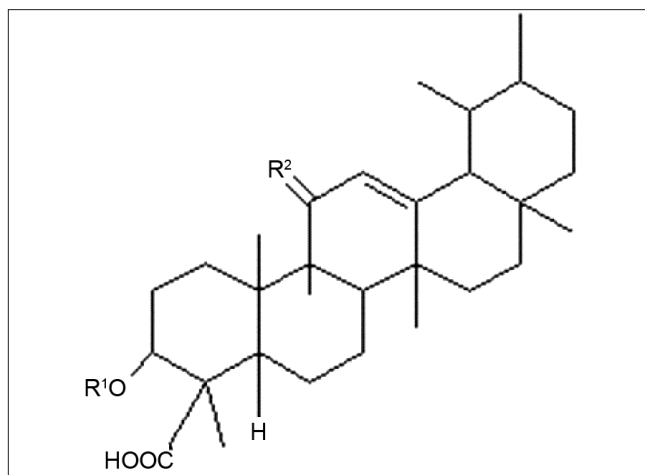


Fig. 1: Structures of four pentacyclic triterpenic acids (Boswellic acids)
 β -Boswellic acid, $R_1=H$, $R_2=H$; acetyl- β -boswellic acid, $R_1=Ac$, $R_2=H$; 11-keto- β -boswellic acid, $R_1=H$, $R_2=O$; acetyl-11-keto- β -boswellic acid, $R_1=Ac$, $R_2=O$.

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

Properties	β -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 $-H_2O$]); 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 $-H_2O$]); 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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Review

Effects of Frankincense Compounds on Infection, Inflammation, and Oral Health

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Abstract: *Boswellia* trees, found throughout the Middle East and parts of Africa and Asia, are the source of frankincense oil. Since antiquity, frankincense has been traded as a precious commodity, but it has also been used for the treatment of chronic disease, inflammation, oral health, and microbial infection. More recently, the bioactive components of *Boswellia* trees have been identified and characterized for their effects on cancer, microbial infection (especially infection by oral pathogens), and inflammation. Most studies have focused on cell lines, but more recent research has also investigated effects in animal models of disease. As natural products are considered to be safer than synthetic drugs, there is growing interest in further developing the use of substances such as frankincense oil for therapeutic treatment.

Keywords: inflammation; oral health; frankincense; infection; microbiology; immunology



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1. Introduction

The increasing rate of antibiotics drug resistance, the cost of drugs, and the lack of access to healthcare systems for many people [1,2], especially in less developed countries, support the need for studying traditional medicines for sustainable, cost-effective therapeutic purposes. Frankincense is one of the common sources for traditional medicine [3]. The word “frankincense” is derived from an old French term “franc encens” and means “pure incense” or “pure and noble high-quality incense”. [4] Traditionally, frankincense gum has been burned for the pleasant fragrance it produces. It can be produced as a hardened resin or gum-like material discharged by the *Boswellia sacra* Flück. tree through cuts made in the trunk. Figure 1 shows the *B. sacra* tree, a member of the *Boswellia* genus. Frankincense has been traded and used as one of the most valuable materials since the beginning of written history [5].

The *Boswellia* genus includes around thirty species and is usually found in the arid regions of tropical Africa, the Arabian Peninsula, and South Asia [6], where moisture is supplied by morning mist. For example, *Boswellia serrata* Roxb. is found in India, *Boswellia sacra* in the Arabian Peninsula, *Boswellia papyrifera* (Caill. ex Delile) Hochst. and *Boswellia rivae* Engl. in Ethiopia, *Boswellia neglecta* S.Moore in Eritrea, and *Boswellia carterii* and *Boswellia frereana* Birdw. in North Africa and Somalia [7]. However, frankincense is obtained mostly from *B. frereana*, *B. sacra*, *B. papyrifera*, and *B. serrata*, which grow in Somalia,

Yemen, Oman, India, and Pakistan [8]. Although many *Boswellia* species are known to produce frankincense, *B. serrata* (India), *B. sacra* (Oman), and *B. carterii* (Somalia) are the major sources of commercial frankincense [9]. Table 1 includes a comprehensive list of all species of *Boswellia* trees as of 17 June 2022, according to The World Flora Online [10], and their geographical distribution [11].



Figure 1. *Boswellia sacra* in Wadi Dawkah, a natural park of frankincense-producing trees in Oman. *Boswellia sacra* photo from Wikimedia.org.

The oleoresin from the *Boswellia* trees has been considered as a treasure for more than a millennium due to its aromatic and medicinal applications [4]. Frankincense resin is secreted as a milky-white, sticky liquid when the plant is injured, and it is also known as olibanum [12]. Olibanum is produced mainly by four different species of *Boswellia*, which are *B. serrata*, *B. carterii*, *B. frereana*, and *B. sacra* [12,13]. The oleo gum resin produced by members of the genus *Boswellia* helps the plant defend against various infections and pests [14] and has been used in religious ceremonies, perfume production, and as a phyto-medicine since antiquity [15]. Recently, the essential oils derived from frankincense are gaining high economic importance internationally for aromatherapy and perfumery [16].

For the present review, the PubMed database, Google Scholar database, Google database, the “Britannica” website, Science Direct, and “The World Flora Online” website were searched using terms that included “frankincense”, “boswellic acids”, and “frankincense and oral pathogens”. Exclusion criteria were non-English-language papers. With the present review, we aim to summarize the most recent research on the effects of frankincense compounds on microbial infection and inflammatory diseases. The effects of frankincense compounds on oral microbial infection are a focus of this review since there is a strong link between systemic and oral health [17].

Table 1. List of the current scientific name, official tree name, synonyms, geographical distribution, and references according to the “The World Flora Online website”.

Current Scientific Name	Official Tree Name	Synonyms	Geographical Distribution	References
<i>Boswellia sacra</i>	<i>Boswellia sacra</i> Flueck.	<i>Boswellia bhaw-dajiana</i> Birdw. <i>Boswellia bhaw-dajiana</i> var. <i>serrulata</i> Engl. <i>Boswellia carteri</i> Birdw. <i>Boswellia carteri</i> var. <i>Subintegra</i> Engl. <i>Boswellia carteri</i> var. <i>Undulatocrenata</i> Engl. <i>Boswellia</i> <i>undulatocrenata</i> (Engl.) Engl.	Arabian Peninsula (Oman, Yemen)	[18]
<i>Boswellia serrata</i>	<i>Boswellia serrata</i> Roxb. Ex Colebr.	<i>Boswellia balsamifera</i> Spreng. <i>Boswellia glabra</i> Roxb. <i>Boswellia thurifera</i> Roxb. Ex Fleming <i>Chloroxylon dupada</i> Buch.-Ham.	India	[19]
-	<i>Boswellia odorata</i> Hutch.	-	Niger, northern Nigeria, and eastern Cameroon	[20]
-	<i>Boswellia popoviana</i> Hepper	-	Socotra	[21]
-	<i>Boswellia ruspoliana</i> Engl.	-	Ethiopia, Somalia, Kenya	[22]
<i>Boswellia socotrana</i>	<i>Boswellia socotrana</i> Balf.f.	-	Socotra	[23]
-	<i>Boswellia holstii</i> Engl.	-	Ethiopia, Somalia, Kenya	[24]
-	<i>Boswellia microphylla</i> Chiov.	-	Ethiopia, Somalia, Kenya	[25]
-	<i>Boswellia multifoliolata</i> Engl.	-	Ethiopia, Somalia, Kenya	[26]
<i>Boswellia nana</i>	<i>Boswellia nana</i> Hepper	-	Socotra	[27]
<i>Boswellia ogadensis</i>	<i>Boswellia ogadensis</i> Vollesen	-	Ethiopia	[28]
<i>Boswellia ovalifoliolata</i>	<i>Boswellia ovalifoliolata</i> N.P.Balakr. & A.N.Henry	-	India	[29]
<i>Boswellia pirottae</i>	<i>Boswellia pirottae</i> Chiov.	-	Ethiopia	[30]
<i>Boswellia ameero</i>	<i>Boswellia ameero</i> Balf.f.	-	Socotra	[31]
-	<i>Boswellia boranensis</i> Engl.	-	Ethiopia, Somalia, Kenya	[32]
-	<i>Boswellia bricchettii</i> (Chiov.) Chiov.	-		[33]
-	<i>Boswellia bullata</i> Thulin	-	Socotra	[34]
-	<i>Boswellia chariensis</i> Guillaumin	-	Ethiopia, Eritrea, Sudan	[35]
-	<i>Boswellia dioscoridis</i> Thulin	-	Socotra	[36]
<i>Boswellia elongata</i>	<i>Boswellia elongata</i> Balf.f.	-	Socotra	[37]
<i>Boswellia frereana</i>	<i>Boswellia frereana</i> Birdw.	-	Somalia	[38]
-	<i>Boswellia globosa</i> Thulin	-	Somalia	[39]
<i>Boswellia dalzielii</i>	<i>Boswellia dalzielii</i> Hutch.	-	Northern Nigeria	[40]
<i>Ambilobea madagascariensis</i>	<i>Ambilobea madagascariensis</i> (Capuron) Thulin, Beier & Razafim.	<i>Boswellia madagascariensis</i> Capuron	Madagascar	[41]

Table 1. Cont.

Current Scientific Name	Official Tree Name	Synonyms	Geographical Distribution	References
<i>Garuga floribunda</i>	<i>Garuga floribunda</i> Decne.	<i>Boswellia javanica</i> Turcz. <i>Bursera javanica</i> (Turcz.) Baill. <i>Garuga abilo</i> (Blanco) Merr. <i>Garuga clarkii</i> Merr. <i>Garuga littoralis</i> Merr. <i>Garuga mollis</i> Turcz. <i>Garuga pacifica</i> Burkill <i>Garuga pinnata</i> var. <i>mollis</i> Kurz	Southern China, Bhutan, Bangladesh, India, through southeast Asia to the Pacific Islands	[42]
<i>Boswellia papyrifera</i>	<i>Boswellia papyrifera</i> (Caill. Ex Delile) Hochst.	<i>Amyris papyrifera</i> Caill. ex Delile <i>Boswellia occidentalis</i> Engl.	Ethiopia	[43]
<i>Boswellia rivae</i>	<i>Boswellia rivae</i> Engl.	-	Ethiopia	[44]
<i>Boswellia hildebrandtii</i>	<i>Boswellia hildebrandtii</i> Engl.	-	Ethiopia, Somalia, Kenya	[45]
-	<i>Boswellia elegans</i> Engl.	-	Ethiopia, Somalia, Kenya	[46]
<i>Boswellia neglecta</i>	<i>Boswellia neglecta</i> S.Moore.	-	Eritrea	[47]

WFO: The World Flora Online.

2. Description of Frankincense Resins, Oils, and Boswellic Acids

The resin is available in yellowish, bluish, and greenish shades, and is composed of 3–8% volatile oils containing various terpenes and sesquiterpenes, 60–70% resin, and 27–35% gum [48]. In the mid-twentieth century, it was found that the gum contains two types of polysaccharides [49]. More recently, the composition showed that the monosaccharides present were predominantly galactose, arabinose, and glucuronic acid, along with small amounts of rhamnose and glucose [50]. However, recent scientific advancements allow us to identify the molecular content of diverse frankincense products such as incense mixtures, components of conventional medicines, and archaeological specimens.

The concentrated volatile, aromatic liquid obtained from different parts of the plant such as roots, seeds, leaves, flowers, and resins is called an essential oil. Mostly, a distillation process is used to extract the essential oil from *Boswellia* plants [51]. The main chemical constituents of frankincense oil are pentacyclic triterpenoids [52], tetracyclic triterpenoids [53], and a variety of other oils [54]. The most common characteristic and intensely studied component in frankincense are the pentacyclic triterpenoids [7,55].

The major active components of frankincense are the boswellic acids (BA), which are extracted from the woody parts of different *Boswellia* trees. The representative phytochemicals are β -boswellic acid, acetyl- β -boswellic acid (ABA), 11-keto- β -boswellic acid (KBA), 3-acetyl-11-keto- β -boswellic acid (AKBA), α -boswellic acid, and acetyl- α -boswellic acid. Figure 2 shows the chemical structure of the main BA.

The chemical composition and yield vary according to different factors such as the geographical region of the tree, the wood surface area, the collection season, the collection method, the age of the tree, and the storage conditions [56]. For instance, the gum resin from *B. serrata* has relatively similar quantities of 11-keto- β -boswellic acid (3–4.7%) and acetyl-11-keto- β -boswellic acid (2.2–2.9%) [7]. However, the resin from *B. carterii* contains 0.5% 11-keto- β -boswellic acid and 3.3% acetyl-11-keto- β -boswellic acid [7].

The gum resin of *B. carterii* reported from Somalia has α -thujene (19.2%), sabinene (9.4%), limonene (7.8%), and α -pinene (7.2%) as the main constituents [57]. This is a native plant of the Red Sea region of North-East Africa, where it is abundant in Somalia and Ethiopia. Other studies on the composition of the oleo resin reported different components in different concentrations. For instance, Wahab reported that the oil contains 62.1% esters, 15.4% alcohols, 9.9% monoterpene hydrocarbons, and 7.1% diterpenes [58], and Wang et al. reported octyl acetate (60.0%), octanol (12.7%), and *p*-cymene (8.7%) [59]. The gas

chromatography–mass spectrometry (GC/MS) analysis of the hydro-distillate of *B. carterii* resin showed the presence of 40 different constituents. The major constituents were verticicol (14.48%), isobutylcyclopentane (12.25%), *n*-octyl acetate (9.20%), and 9-oxabicyclo-[6.1.0]-non-3-yne (9.12%) [60]. However, the composition of the resin differs due to different factors such as climate, geography, season of the year, and the extraction conditions. This notion is corroborated by a report from Chen et al. (2013) which observed low concentrations of the above components [61], while other studies reported higher concentrations of *n*-octyl acetate [61,62].

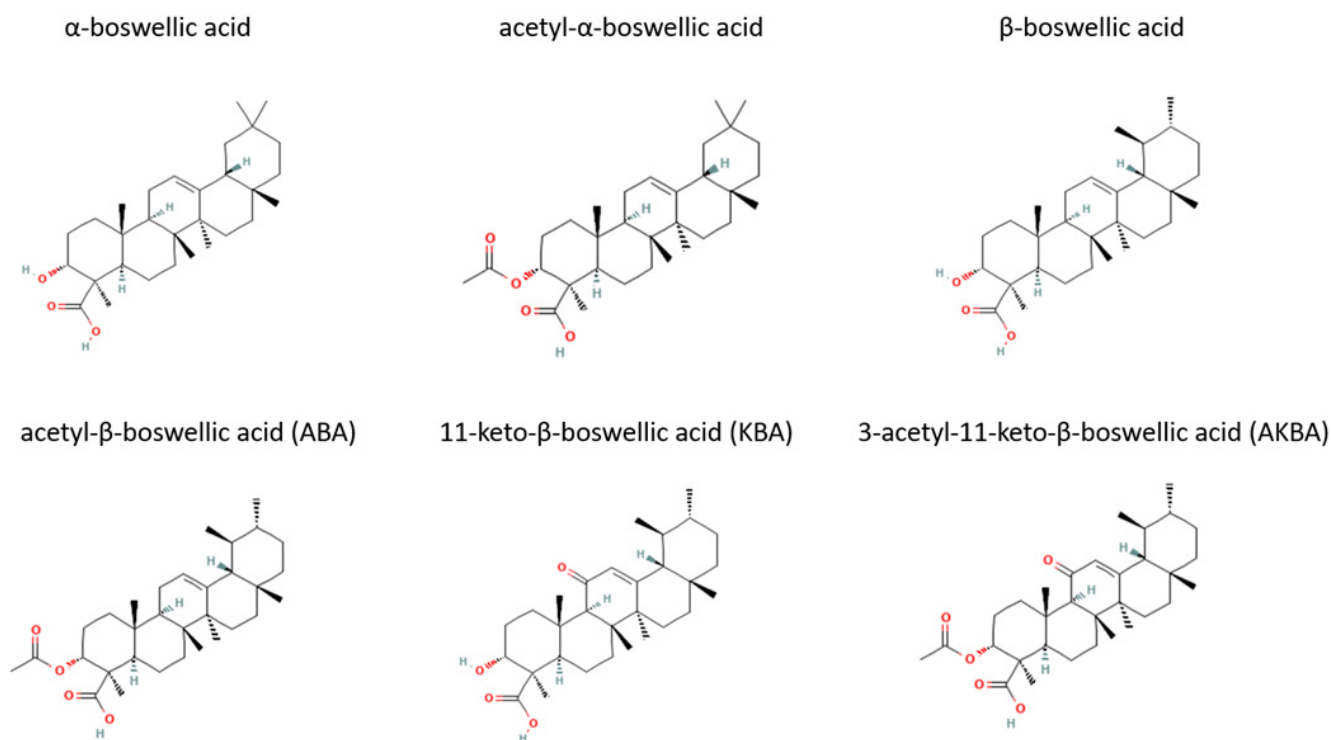


Figure 2. Chemical structure of common boswellic acids found in frankincense. Two-dimensional chemical structures were obtained from Pub Chem. Pub Chem CIDs are as follows: α -boswellic acid, 637234; acetyl- α -boswellic acid, 15181201; β -boswellic acid, 168928; acetyl- β -boswellic acid (ABA), 11386458; 11-keto- β -boswellic acid (KBA), 9847548; 3-acetyl-11-keto- β -boswellic acid (AKBA), 11168203.

Boswellia dalzielii, which grows in West Africa, is an understudied species. However, a study conducted using essential oil from 21 oleoresin samples from northern Nigeria and two samples from Ghana revealed that α -pinene was the dominant component (21.7–76.6%), followed by α -thujene (2.0–17.6%), myrcene (up to 35.2%), *p*-cymene (0.3–15.6%), and limonene (1.1–32.9%) [63]. It was reported that out of the 29 compounds obtained from the essential oil from leaves, α -pinene was the dominant component (45.7%) [64]. On the other hand, it was also reported that out of 50 compounds isolated, δ -3-carene (27.7%) was the dominant one [65]. The most abundant chemical components and the type of *Boswellia* plant sources are summarized in Table 2.

Table 2. Prominent features of compounds in frankincense resin and oils.

Frankincense Type	Country of Origin	Source	Chemical/Active Component	References
<i>Boswellia dalzielii</i>	Chad, Mali, Nigeria	Hydro-distilled leaf essential oil	δ -3-carene (27.7%), α -pinene (15.2%), <i>p</i> -cymene (9.5%), β -phellandrene (8.5%), isolongifolene (6.2%), and myrcene (5.7%).	[65]
<i>Boswellia dalzielii</i>	Nigeria	Hydro-distilled leaf essential oil	α -pinene (45.7%) and α -terpinene (11.5%), trans-sabinene hydrate (4.6%), cis-p-menth-2-en-1-ol (2.9%), α -campholenal (2.7%), caryophyllene oxide, and α -phellandrene (2.3%)	[64]
<i>B. carterii</i>	Somalia	Gum resin	Esters (62.1%), 1-octyl acetate being predominant (60.0%). Alcohols amount to 15.4%, 1-octanol being the major component (12.7%), and diterpene constituents amount to 7.1%, including cembrene (1.4%), isocembrene (1.8%), incensole (2.7%), and isoincensole (0.8) and a mixture of monoterpene hydrocarbons which amounts to 9.9%.	[58]
<i>B. rivae</i>	Ethiopia	Essential oil from frankincense	α -Pinene (36.1–67.7%), δ -3-carene (12.2%), and limonene (12.0%).	[66]
<i>B. neglecta</i>	Ethiopia	Essential oil from frankincense	α -Pinene (36.1–67.7%), terpinen-4-ol (11.3%).	[66]

3. Modern Medicinal Uses of Frankincense

Many plant components from *Boswellia* are used to treat chronic diseases with comparatively few side effects [67,68]. Indian traditional medicine practice narrates that *Boswellia* decoctions were used to treat various gastrointestinal tract conditions such as diarrhea, flatulence, alimentary stoppage, and vomiting [69–72]. It was believed that the decoctions contain active ingredients from *Boswellia*, which are useful in treating the above-mentioned diseases. Furthermore, the extract was used to treat bronchitis, asthma, hoarseness, dyspnea, cough, and cold [73,74].

The gum extracts or resins from *Boswellia* sp. and their triterpenes, especially BA, have attracted the attention of pharmacologists, medicinal chemists, and biochemists as therapeutic agents due to their efficacy in treating rheumatoid arthritis and chronic inflammation without side effects and toxicity. The gum exudate obtained from the bark of the tree *B. serrata*, also called Indian olibanum, has been extensively used in the treatment of arthritis, asthma, ulcers, and skin diseases by practitioners of Indian traditional medicine [48,58]. It has also been widely used in various formulations for the treatment of inflammation related disorders in the past decade [48,75]. One study analyzed the effects of gum resins of *B. serrata* (900 mg daily divided in three doses for 6 weeks) on human patients suffering from chronic colitis [67,76]. The authors found that out of 20 patients treated with *Boswellia* gum resin, 18 patients showed an improvement in one or more parameters, including stool properties, histopathology and scanning electron microscopy characterization, hemoglobin, serum iron, calcium, phosphorus, proteins, total leukocytes, and eosinophils [67,76]. The control group (10 patients) was given sulfasalazine at a dose of 1 g three times a day for 6 weeks. The authors reported that 6 out of 10 patients in the control group showed similar improvements with the same parameters tested in the *B. serrata* group. This study demonstrates that a gum resin preparation from *B. serrata* might be effective in the treatment of chronic colitis, with minimal side effects [67,76]. The same research group evaluated the effects of *B. serrata* gum resin on the treatment of patients with bronchial asthma [74]. Their data demonstrated that 70% of patients treated with 300 mg thrice daily for 6 weeks showed improvement of disease, evident by the disappearance of physical symptoms and signs such as dyspnea, rhonchi, number of attacks, as well as

a decrease in eosinophilic counts. The control group (treated with placebo) only showed 27% of improvements in symptoms [74]. These data imply that gum resin from *B. serrata* could serve as a pharmacological agent in the treatment of bronchial asthma.

Gum resin from *B. serrata* was reported to be a potential remedy for inflammation, and it has been used as a folk medicine for topical and systemic inflammatory diseases for centuries [48]. The oleo gum resin of *B. carterii* has been used in folk medicine to treat cough and asthma and as an embalming fluid for human corpses. In addition, it has been used as an incense, respiratory antiseptic, and diuretic stimulant [58].

The oleo gum resin of *B. serrata* and *B. carterii* were also used in traditional medicine in different countries to treat rheumatic and other inflammatory diseases, including Crohn's disease and ulcerative colitis [76–78]. However, *B. serrata* was reported to be the least effective in recurrent infections [79]. In addition, frankincense extracts and oils were used as antiseptic agents in mouthwash and also used to treat cough and asthma [77]. Furthermore, recent studies on animals and humans have demonstrated the efficacy of resin gum of *B. serrata* to treat inflammatory bowel disease, asthma, osteoarthritis, and rheumatoid arthritis [76,80,81].

Though frankincense has been known for its medicinal properties since antiquity, it is still widely used in modern medical treatment. In 2010, Moussaieff and Mechoulam reviewed *Boswellia* resin constituents in vitro, in vivo, and in clinical trials studies [82]. Indeed, in Ayurvedic medicine, different parts of the *Boswellia* tree and derived extracts are used for the treatment of respiratory, gastrointestinal, immune system, and skin conditions. Most of the published work focuses on the pharmacological activities of boswellic acids, specifically on their anti-inflammatory, analgesic, and anti-arthritic properties. As an example, there is growing evidence to support the clinical efficacy of *Boswellia* in osteoarthritis patients. However, there is inadequate evidence to demonstrate the clinical efficacy in rheumatoid arthritis patients [83]. The application of frankincense to treat different diseases of recent times is discussed below and summarized in Figure 3. Frankincense has been used to treat both infections and chronic diseases.

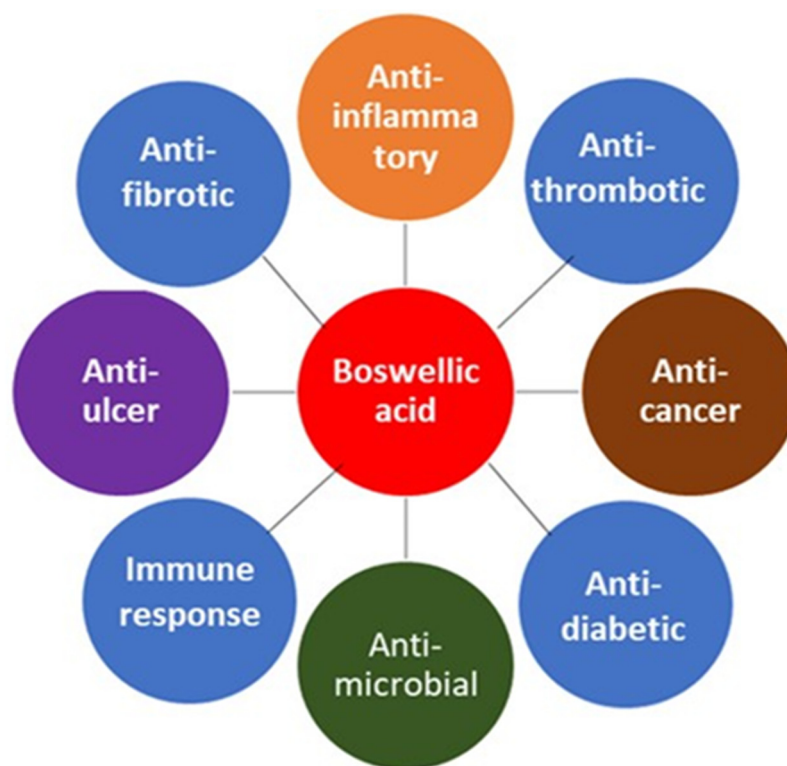


Figure 3. Modern medicinal uses of *Boswellia*.

3.1. Anti-Cancer

BA is one of the most extensively studied naturally occurring anti-cancer agents due to its anti-carcinogenic, anti-tumor, and anti-hyperlipidemic activities [4,84]. An in vitro study isolated five terpenoids from the gum resin of *B. carterii* and showed that three different compounds exhibited moderate cytotoxic effects against three human cancer cell lines [85]. The isolated compounds (named compounds 1–5) were chemically characterized, and their IC₅₀ values against all three cell lines were described in the study [85]. Among the five compounds, compound 3 showed the following IC₅₀ values: $49.84 \pm 3.23 \mu\text{M}$ (against HepG2 cells, human hepatocellular carcinoma), $57.05 \pm 7.85 \mu\text{M}$ (against A549 cells, human lung carcinoma), and $75.49 \pm 7.80 \mu\text{M}$ (against MCF-7 cells, human breast cancer) [85]. All these values can be compared with IC₅₀ for cisplatin (a chemotherapy drug used to treat several types of tumors): $23.44 \pm 3.30 \mu\text{M}$ (against HepG2 cells), $18.32 \pm 3.55 \mu\text{M}$ (against A549 cells), and $21.42 \pm 7.57 \mu\text{M}$ (against MCF-7 cells) [85]. Even though compound 3 showed promising results, cisplatin was still more effective against the human cancer cell lines. Future studies might determine if the cisplatin and frankincense compounds have synergistic cytotoxic effects against human cancer cells.

AKBA and KBA are the key players involved in the cytotoxic effects of BAs. They inhibit topoisomerase I and IIa, which results in the inhibition of cell growth and proliferation by inducing apoptosis via a caspase-8-dependent pathway in human leukemia, colon, hepatoma, and in various other cancer cell lines in vitro [86,87]. IC₅₀ values for boswellic acid essential oils were calculated and showed that essential oil hydro-distilled at 100 °C produced more potent cytotoxic effects [86]. The IC₅₀ values for T47D cells were 900 and 1450 dilutions for essential oils obtained at 78 °C and 100 °C, respectively. Among the cancer cell lines tested in this study, MCF-7 cells were the most sensitive to essential oils with suppressed cell viability [86]. Boswellic acid acetate inhibited cell growth in vitro in a dose-dependent manner with IC₅₀s of 5.8, 8.7, 7.3, 6.2, 9.8, and 6.6 $\mu\text{g/mL}$ in NB4, SKNO-1, HL-60, U937, K562, and ML-1 cells at 4 days of treatment, respectively [87].

BAs also inhibit protein synthesis by interacting with ribosomal proteins, and thus control cancer development [88]. A study using human colon cancer cells in vitro suggested that *B. serrata* extracts inhibit proliferation, angiogenesis, and migration, and induces apoptosis of the cells by decreasing PGE2 levels [89].

3.2. Hypolipidemic and Hypoglycemic Effects

Animal studies have shown that the water-soluble fraction of *Boswellia* is effective in reducing the total cholesterol levels [90]. Extracts of *B. serrata* gum resins can reduce serum cholesterol levels and increase heavy-density lipoproteins (HDL) in rats [90]. In another study, *Boswellia* extracts significantly increased blood HDL levels and, remarkably, decreased blood low-density lipoprotein (LDL) levels, as well as the levels of liver enzymes SGPT and SGOT in patients after six weeks of treatment with *Boswellia* [91]. In contrast, the use of *B. serrata* gum resin for eight weeks at a relatively high dose did not lower glucose and lipid levels in diabetic patients [92].

Several studies have revealed that *Boswellia* gum resin has high hypolipidemic and hypoglycemic effects. Both BA and KBA reduced hyperglycemia and improved biochemical parameters such as the lipid profile. The strong anti-diabetic activity of β -BA and β -KBA was shown by treatments with different concentrations (1, 2, and 10 mg/kg body weight) for 21 days. This treatment significantly improved body weight loss, water consumption, and the concentration of blood glucose levels in diabetic animals [93]. Azemi et al. suggest that the use of appropriate doses of *B. serrata* extracts is vital in obtaining an anti-hyperglycemic effect on blood sugar and also in preventing complications of diabetes [94].

The effect of *Boswellia* resin on metabolic syndromes has been recently reviewed [95]. The extensive literature analysis of animal and human studies revealed that the resin's protective and therapeutic effects are due to a decrease in hyperglycemia, hyperlipidemia, hypertension, and obesity. The authors refer the readers to this recent review for more details on the proposed mechanisms involved [95].

4. Antimicrobial Activity of Frankincense

In general, the bioactive natural compounds produced by different plants are considered better alternatives to synthetic antimicrobial and antioxidant agents. Different compounds obtained from *Boswellia* resins, particularly BA and their derivatives, exhibited diverse biological activities. As considered in this section, the antimicrobial effects can vary depending on the study and the amount of bioactive compounds present in the frankincense extracts.

4.1. Activity of *Boswellia* against Microbes

A study analyzed the antimicrobial and antioxidant activities of methanol extract, ethyl acetate extract, and essential oil from *B. carterii* resin [60]. The methanol extract exhibited the highest antimicrobial activity (MIC of 25 µg/mL) against different Gram-positive bacteria such as *Bacillus subtilis*, *B. circulans*, and *Streptococcus faecalis*, and a moderate MIC of 400 µg/mL against the Gram-positive *Listeria monocytogenes*, Gram-negative bacteria such as *Escherichia coli* (MIC of 25 µg/mL) and *Pseudomonas aeruginosa* (MIC of 300 µg/mL), and two yeasts, *Candida albicans* (MIC of >1000 µg/mL) and *Saccharomyces cerevisiae* (MIC of 25 µg/mL), compared with essential oil from *B. carterii* resin [60]. The ethyl acetate extract also showed favorable results, with MIC values ranging from 25 to >1000 µg/mL. The IC₅₀ values for the methanol extract, ethyl acetate extract, and essential oils were 5.78, 7.66, and 15.21 mg/mL, respectively [60]. The methanol and ethyl acetate extracts displayed the highest antimicrobial activity against *S. faecalis*, *B. subtilis*, and *B. circulans* [60].

The antimicrobial activity of the essential oils obtained from the hydro distillation of the barks of *B. dioscoridis*, *B. elongata*, and *B. socotrana* were investigated against two Gram-positive (*Staphylococcus aureus* and *B. subtilis*) and two Gram-negative (*E. coli* and *P. aeruginosa*) bacterial species, as well as against *C. albicans*. The essential oils exhibited different levels of inhibition against the bacterial strains but not against *C. albicans*. The antimicrobial effects of the essential oils showed MIC of approximately 3–17 mg/mL compared with the use of conventional antibiotics (amoxicillin, gentamicin) and antifungals (nystatin) that showed MIC of approximately 3.5–7 µg/mL [96]. In general, Gram-positive strains exhibited higher susceptibility to the essential oils than Gram-negative strains. *B. socotrana* essential oil showed the highest antibacterial activity against *S. aureus* and *B. subtilis* [96].

The oleo gum resin essential oils from *B. carterii* (Somalia), *B. papyrifera* (Ethiopia), *B. serrata* (India), and *B. rivae* (Ethiopia) were individually tested against different fungi and Gram-positive and Gram-negative bacteria. The essential oils exhibited significant antifungal activity against both *C. albicans* and *C. tropicalis*, with the essential oils from *B. carterii* and *B. papyrifera* showing the best activity [97]. The MIC values for *C. albicans* and *C. tropicalis* were 12.86 and 12.86 µg/mL (*B. serrata*), 6.16 and 6.16 µg/mL (*B. carterii*), 6.09 and 6.09 µg/mL (*B. papyrifera*), and 2.65 and 27.38 µg/mL (*B. rivae*), respectively, compared with the MIC of 0.15 µg/mL for amphotericin B. The essential oil of *B. rivae* resin exhibited the best activity against *C. albicans* [97]. Limonene present in the essential oils is thought to be responsible for the antifungal activity [98], since oleo gum resin essential oils without limonene lack antifungal activity. The oleo gum resins also showed significant antibacterial effects against Gram-positive *S. aureus* and *S. epidermidis*, with MIC values ranging from 3.52 to 107.20 µg/mL. These values can be compared with the MIC of 1 µg/mL for vancomycin and 2 µg/mL for amikacin used as controls in the experiments [97]. The frankincense compounds against Gram-negative *E. coli* and *P. aeruginosa* showed MIC ranging from 6.60 to 107.18 µg/mL, compared to the vancomycin MIC of 10 and 5 µg/mL for *E. coli* and *P. aeruginosa*, respectively. It is noteworthy that some of the frankincense compounds had antimicrobial effects at concentrations that were comparable or very close to concentrations of the standard antibiotics used in the in vitro experiments. Future studies might confirm and expand the results to in vivo and clinical models.

Oils extracted from the resins of three *B. sacra* cultivars (Najdi, Sahli, and Houjri) were tested for their antimicrobial activities. Grade 1, grade 2, and grade 3 essential

oils were prepared from each cultivar. Najdi grade 2 essential oil exhibited antibacterial activity against *S. aureus* and *P. aeruginosa*. The grade 2 essential oils of Sahli and Houjiri were effective against *Propionibacterium acnes* (a dermatological strain). All the essential oils displayed significant antifungal activity in vitro against *C. albicans* and *Malassezia furfur* [99]. Hence, essential oils from *B. sacra* should be further investigated as potential anti-staphylococcal and anti-pseudomonal therapeutic agents.

The antimicrobial activity of *B. carterii* essential oil was investigated against *E. coli*, *P. aeruginosa*, and three strains of *S. aureus*. The oil displayed inhibitory activity against all the pathogens tested. The highest activity was noted against *P. aeruginosa* [97]. However, Chao et al. (2008) reported that *B. carterii* essential oil does not have an inhibitory effect against methicillin-resistant *S. aureus* (MRSA) [100]. Further experiments are needed to resolve the apparent discrepancy.

A study was conducted to investigate the antimicrobial property of essential oils from frankincense and myrrh in independent and combined forms. Essential oils from *B. rivae*, *B. neglecta*, and *B. papyrifera* and myrrh and sweet myrrh, *Commiphora guidotti* and *Commiphora myrrha*, were used in this study. *Cryptococcus neoformans* and *P. aeruginosa* were the most susceptible to oils of both *Boswellia* and *Commiphora* spp, with MIC values ranging between 0.80 and 1.40 mg/mL for *C. neoformans*, and 0.50 and 1.50 mg/mL, respectively [66]. Noteworthy antimicrobial activity was considered for MIC values ≤ 2.00 mg/mL, as the controls with standard antibiotics showed MIC values ranging between 0.2×10^{-3} and 0.6×10^{-3} mg/mL [66]. The majority (80%) of the oils investigated in this study had significant antimicrobial activity. Different combinations of frankincense and myrrh oils showed that the oils have synergistic properties. Further investigations showed that the most preferable combination against *Bacillus cereus* was *B. papyrifera* and *C. myrrha* [66].

Twenty different frankincense oil samples from various international outlets were analyzed for their chemical components using GC/MS. Though the oils were qualitatively similar, they exhibited quantitative variation. Antimicrobial study was conducted evaluating all the 20 essential oil against five test microorganisms. The antimicrobial effectiveness of the tested oils varied against *S. aureus* depending on the oil sample studied. In this study, it is noteworthy that 6 out of the 20 oil samples tested were considered effective antimicrobials against *B. cereus*. However, moderate to poor activity was observed against *C. albicans* [101].

The effects of *B. sacra* resin, leaf extract, and essential oil on the growth and aflatoxin production by *Aspergillus flavus* and *Aspergillus parasiticus* were studied [102]. Interesting data showed that essential oils from *B. sacra* inhibited the aflatoxin production and the growth of the fungi. However, the resin from *B. sacra* inhibited aflatoxin production but did not impact the growth of the fungi. Nevertheless, the leaf extract of *B. sacra* enhanced aflatoxin production and mycelial dry weight. This study concluded that the resin and essential oil of *B. sacra* could be used as safe preservatives to increase the shelf life of food and feed products.

4.2. Activity of *Boswellia* against Fungal and Bacterial Biofilms

The structured microbial communities attached to a surface are called biofilms. Bacteria, fungi, and protists are capable of forming biofilms. *S. aureus* biofilms are the major cause of device-related infections, which are difficult to treat as the biofilms are generally resistant to conventional antibiotics [103]. Although less frequent, fungal films also develop on implanted medical devices. For instance, *C. albicans*, responsible for causing infections related to indwelling medical devices, is difficult to treat when it forms biofilms because of resistance against most antifungal agents [104,105]. Hence, there is a need to develop new antifungal agents, especially those that target the biofilm stage of the fungi.

B. papyrifera and *B. rivae* essential oils were tested against bacterial biofilms. *B. papyrifera* essential oil showed substantial activity against biofilms formed by both *S. epidermidis* and *S. aureus*. The essential oil of *B. papyrifera* also demonstrated noticeable antimicrobial effects on *S. epidermidis* biofilms. Similarly, *B. rivae* essential oil was effective

tive against preformed *C. albicans* biofilms [106]. The essential oils especially inhibited germ tube formation and thus hyphal formation. The hyphal formation is vital for the virulence, biofilm formation, and structural integrity of *C. albicans* [105,107]. A large part of the inhibitory activity of *B. riva* oleo gum resin oil was shown to be due to the presence of limonene (28%). Hence, further studies are warranted to characterize the antibiofilm activity of other components in the oleo gum resin oil.

4.3. Antimicrobial Activity against Oral Pathogens

Dental caries and periodontitis remain two of the major oral diseases that affect more than half of the global population [108]. Periodontitis is often referred as a common inflammatory disease in humans. Figure 4 shows oral cavities with and without periodontitis. The etiology of these diseases has been linked to certain bacterial species, plaque and biofilm formation, and the resultant inflammatory states. Current therapies for treating periodontal disease place an emphasis on biofilm removal. This is exercised via a combination of mechanical (such as scaling and root planing) and antibiotic treatments. However, these treatment modalities are still unable to fully remove biofilms. This has led to an interest in incorporating herbal extracts into current treatment regimens.



Figure 4. Comparison of healthy and unhealthy gingival tissue. The healthy gingiva is pink in color, while unhealthy gingiva is darker red, and may present bleeding. (Photos from Pixabay.com and Wikipedia.org.)

Many studies have been performed using the resin of *B. serrata*. As noted above, this resin contains boswellic acid, which are the active components in its anti-inflammatory effects. In addition, both the boswellic acid and the essential oils of *B. serrata* exhibit antimicrobial properties. Of the four major boswellic acids, acetyl-11-keto- β -boswellic acid (AKBA), has consistently demonstrated the greatest antibacterial effects. In fact, several studies have determined that AKBA is the most active component in the resin of *B. serrata* and other *Boswellia* species [109].

In terms of antibacterial effectiveness, AKBA isolated from *B. serrata* demonstrated activity against *Streptococcus mutans*, *Enterococcus faecalis*, *Enterococcus faecium*, *Actinomyces viscosus*, *Streptococcus sanguinis*, *Fusobacterium nucleatum*, *Prevotella intermedia*, and *Porphyromonas gingivalis*. Furthermore, the post-antibiotic effects of AKBA were determined to be greater than those of ciprofloxacin, and AKBA was also shown to inhibit biofilms of the cariogenic bacteria *S. mutans* [109].

In a double-blinded, randomized clinical trial, the effectiveness of traditional scaling and root planing methods were compared to the use of *B. serrata* extract or powder [110]. The results indicated that the addition of *B. serrata* extract or powder to traditional scaling and root planing treatments leads to better gingival health as measured by gingival, plaque, and bleeding indices, as well as probed pocket depths [110]. The authors concluded that the anti-inflammatory properties of *B. serrata* extract had results comparable or even superior to traditional scaling and root planing treatments.

In another study contrasting the potencies of different forms of frankincense extract, it was shown that hydro-alcoholic extract from *B. serrata* had greater antimicrobial potency than organic extract [111]. While the hydro-alcoholic extract could successfully inhibit *C. albicans*, *S. mutans*, *C. krusei*, and *C. glabrata*, organic extract could only inhibit *C. glabrata* at a higher concentration than was needed for the hydro-alcoholic extract.

Current periodontal therapies have often utilized synthetic chemical agents, most notably chlorhexidine, as adjunct to mechanical debridement. However, chronic use of such chemical agents can lead to undesirable side effects, including toxicity to connective tissue, staining, dysgeusia, dry mouth, and allergies [112]. Vahabi et al. analyzed the effects of *B. serrata*, *L. inermis*, and *M. sylvestris* on *Aggregatibacter actinomycetemcomitans*, one of the major species implicated in aggressive periodontitis, as possible alternatives to chlorhexidine. Of the three plant extracts, *B. serrata* had the strongest antimicrobial effect [112]. However, its effects were still inferior to those of chlorhexidine and doxycycline. The antimicrobial effects of frankincense against oral pathogens are summarized in Table 3. According to the data summarized in Table 3, AKBA showed stronger antimicrobial effects against oral pathogens (*P. gingivalis*, *P. intermedia*, *E. faecalis*, *S. mutans*, *E. faecium*, *A. viscosus*, *S. sanguinis*). Therefore, future studies should further examine the antimicrobial effects of AKBA on oral pathogens. Given its antibacterial, antifungal, and antioxidant properties, it is not surprising that frankincense also has promising beneficial effects on oral health.

There is growing evidence that BA is a multitarget agent, since it can modulate several molecular targets, such as enzymes, growth factors, kinases, transcription factors, receptors, and other targets related to survival and proliferation of cells [68]. However, to the best of our knowledge, it remains to be determined whether BA affects molecular targets specific to oral tissues that could affect oral microbial infection and diseases. Some of the molecular targets involved in anti-inflammatory diseases affected by BA will be discussed in the next section.

Table 3. Boswellic acid extracts or chemical constituents with antimicrobial activity against oral pathogens in vitro.

Microbe	Extract or Chemical Constituent	MIC ($\mu\text{g/mL}$)	References
<i>Aggregatibacter actinomycetemcomitans</i> ATCC 33384 (Gram-negative)	<i>Boswellia serrata</i>	512	[113]
<i>Aggregatibacter actinomycetemcomitans</i> JP2 NOV99 (Gram-negative)	HAE of <i>Boswellia serrata</i>	78	[112]
<i>Streptococcus mutans</i> ATCC 25175 (Gram-positive)	KBA	16	[109]
	AKBA	2	
	BA	32	
	ABA	>128	
<i>Streptococcus mutans</i> PTCC 1688 (Gram-positive)	HAE of <i>Boswellia serrata</i>	50,000	[111]
<i>Enterococcus faecalis</i> ATCC 29212 (Gram-positive)	KBA	16	[109]
	AKBA	4	
	BA	8	
	ABA	>128	
<i>Enterococcus faecium</i> ATCC 8042 (Gram-positive)	KBA	16	[109]
	AKBA	4	
	BA	8	
	ABA	>128	
<i>Actinomyces viscosus</i> ATCC 15987 (Gram-positive)	KBA	8	[109]
	AKBA	2	
	BA	64	
	ABA	>128	

Table 3. Cont.

Microbe	Extract or Chemical Constituent	MIC ($\mu\text{g/mL}$)	Reference
<i>Streptococcus sanguinis</i> ATCC 10556 (Gram-positive)	KBA	8	[109]
	AKBA	2	
	BA	128	
	ABA	>128	
<i>Fusobacterium nucleatum</i> ATCC 10953 (Gram-negative)	KBA	>128	[109]
	AKBA	>128	
	BA	>128	
	ABA	>128	
<i>Prevotella intermedia</i> ATCC 25611 (Gram-negative)	KBA	16	[109]
	AKBA	4	
	BA	32	
	ABA	>128	
<i>Porphyromonas gingivalis</i> ATCC 33277 (Gram-negative)	KBA	8	[109]
	AKBA	4	
	BA	32	
	ABA	>128	
<i>Candida albicans</i> PTCC 5027	HAE of <i>Boswellia serrata</i>	50,000	[111]

MIC: minimum inhibitory concentration; KBA: 11-keto- β -boswellic acid; AKBA: acetyl-11-keto- β -boswellic acid; BA: β -boswellic acid; ABA: acetyl- β -boswellic acid; HAE: hydro-alcoholic extract.

5. Anti-Inflammatory Effects of Frankincense

Many patients consuming non-steroidal anti-inflammatory drugs (NSAID) suffer from adverse effects of the drugs on the gastrointestinal or cardiovascular systems. Many efforts have been made to develop drugs that avoid these complications, but the goal is still far from being achieved. Hence, it is necessary to search for novel, alternative drugs. In this context, *B. serrata* and other *Boswellia* species have gained prominence as potential alternatives as anti-inflammatory herbal remedies. The anti-inflammatory properties of boswellic acids have been well-established by several studies with cells in vitro, and preclinical, and clinical trials [4,7].

Studies on animals and humans have shown the anti-inflammatory potential of *B. serrata* gum resin to treat different inflammatory disorders such as inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, and asthma [80]. Corticosteroids are essential to control cerebral edema but they also cause severe negative impacts. In contrast, the gum resin of *B. serrata* was found to control the peritumoral brain edema associated with glioma [114].

The anti-inflammatory activity of *B. serrata* is due to the presence of α - and β -boswellic acid and other pentacyclic triterpenic acids. These compounds inhibit pro-inflammatory processes by acting on 5-lipoxygenase and cyclo-oxygenase and on the complement system [73,115,116]. Inhibition of prostaglandin synthesis plays only a minimal role in the anti-inflammatory effect of BAs. However, inhibition of 5-lipoxygenase by BA decreases production of leukotrienes, whereas chronic inflammatory diseases are associated with increased leukotriene activity [115].

BA is involved in the inhibition of inflammation induced by factors such as histamine, prostaglandins, leukotriene, 5-lipoxygenase, human leukocyte elastase, cytokines, tumor necrosis factor, and free oxygen radicals. Figure 5 summarizes the inhibitory effects induced by BAs. To demonstrate the anti-inflammatory activity of the gum resin of *Boswellia* species, experiments were conducted in animal models. Carrageenan-induced mouse paw edema and rat pleurisy models were employed to test the effectiveness of defined BAs in vivo. This study also demonstrated the suppression of PGE₂ formation by BAs via interference with mPGES1, which may represent a biochemical basis for the anti-inflammatory effectiveness of BAs [117].

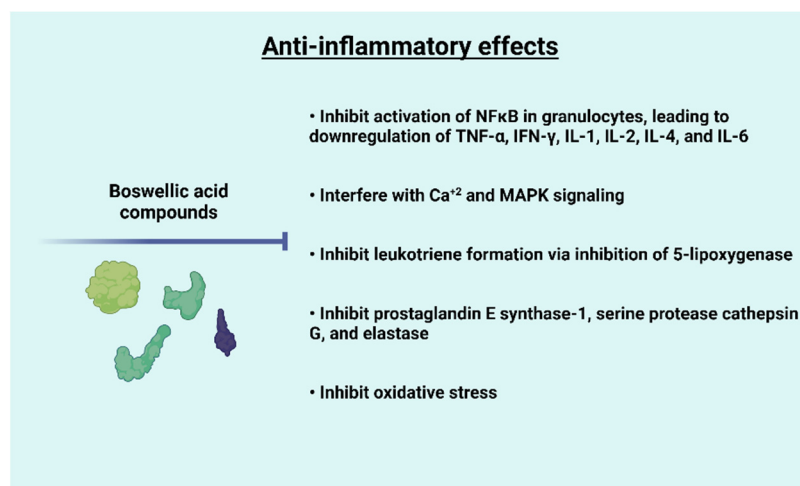


Figure 5. Schematic diagram showing anti-inflammatory effects of boswellic acids and *Boswellia* extracts.

Some limitations of this study must be considered. First, more studies are required to elucidate the antimicrobial and anti-inflammatory mechanisms exerted by frankincense extracts and compounds. Secondly, more studies, including pre-clinical and randomized clinical trials, are needed to better understand the beneficial effects of frankincense extracts and compounds on human health. For more details on the pre-clinical and clinical activities of frankincense, we refer the readers to the recent reviews by Efferth and Oesch [4] and by Hussain et al. [118].

To the best of our knowledge, some limitations to large-scale application of frankincense compounds for clinical studies could be the lack of efficiency in the synthetic methodology for industrial production, and the sustainability of growing enough *Boswellia* trees [118]. According to Groenendijk et al. [119], over the next five decades, the population of *B. papyrifera* trees will decrease to about 10% of its present population due to over-exploitation in harvesting the tree [118].

6. Concluding Statement

Boswellia trees and natural products derived from the trees have been used since antiquity for the treatment of chronic disease, inflammation, and infection. The identification of the bioactive components of frankincense will allow the characterization of the molecular and cellular basis for their therapeutic effects, and the incorporation of these compounds into products that could be marketed for use in treatment for cancer and inflammation and improvement of oral health.

This review highlights the chemical compounds (boswellic acids) isolated from *Boswellia* gum resins and their potential antimicrobial, anti-tumor, and anti-inflammatory effects. The beneficial role of *Boswellia* gum resins in treating chronic diseases, such as colitis and bronchial asthma, in small studies including human patients, demonstrate the potential of frankincense for treatment in the clinical setting. However, more studies including a higher number of subjects and clinical trials are needed to confirm and expand our knowledge of the use of frankincense for treatment of chronic diseases.

Furthermore, this review discussed the antimicrobial effects of several active compounds of frankincense. Given the high cost of antibiotic therapy and the increase in antibiotic resistance, more research is needed on the potential antimicrobial effects of natural products. We focused on the most recent discoveries of the beneficial effects of frankincense compounds against oral pathogens, given the important connection between oral and systemic health [17].

Gum resin of *Boswellia* is included in the list of substances Generally Recognized As Safe (GRAS), which allows its use as a food additive by the U.S. FDA [109]. One could

easily envision the incorporation of frankincense and some of its components such as BAs into mouthwashes and toothpaste, and into topical ointments for inflammatory disorders of the skin.

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COSA DOVRESTI SAPERE SULLA PROSTATITE

Urology Care
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CHE COS'È LA PROSTATA?

La prostata è una piccola ghiandola a forma di noce che fa parte del sistema riproduttivo maschile. Il compito principale della prostata è quello produrre il liquido seminale, che protegge e trasporta gli spermatozoi.

CHE COS'È LA PROSTATITE?

La prostatite è comunemente associata a dolore a livello della zona pelvica che origina dalla prostata. Può manifestarsi negli uomini a qualsiasi età ed essere causata da:

- un'infezione batterica
- un'infiammazione (tessuto doloroso, rosso e gonfio) dovuta a una lesione o a un'infezione
- altri problemi

QUALI SONO I SINTOMI DELLA PROSTATITE?

Descrivere come ti senti è fondamentale per aiutare il tuo medico a diagnosticare il tipo di prostatite.

La prostatite cronica / sindrome da dolore pelvico cronico (PC/DPC) è un'infiammazione della prostata e dei nervi presenti in quest'area. Il dolore da PC/DPC può durare da alcune settimane a mesi. NON si tratta di un'infezione.

I sintomi della prostatite sono:

- difficoltà a urinare, a volte accompagnata da dolore durante la minzione
- dolore nella zona circostante la vescica, i testicoli, il pene e/o l'ano
- dolore durante l'eiaculazione

La prostatite batterica cronica è di natura batterica e meno frequente. Tende a ripresentarsi ciclicamente per lunghi periodi di almeno tre mesi.

I sintomi possono essere:

- sensazione di bruciore durante la minzione
- bisogno di urinare spesso (8 o più volte al giorno)
- dolore nella zona circostante la vescica, i testicoli, il pene e/o l'ano
- dolore durante l'eiaculazione

La prostatite batterica acuta è anch'essa di natura batterica e meno frequente. I sintomi possono insorgere all'improvviso ed essere molto dolorosi. Per questo motivo richiede fin da subito l'assistenza medica.

I sintomi includono:

- brividi
- febbre
- minzione molto dolorosa
- difficoltà a urinare

La prostatite non batterica può essere causata da stress, irritazione nervosa, lesioni o infezioni del tratto urinario. Non viene riscontrata la presenza di batteri nelle urine o nello sperma.

QUALI SONO LE CAUSE DELLA PROSTATITE?

La causa della prostatite non è sempre chiara. Alcuni fattori possono aumentare il rischio di contrarre un'infezione batterica, ad esempio un'infezione trasmessa per via

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sessuale, un catetere, un'infezione alla vescica o un problema al tratto urinario.

Non sempre il dolore pelvico è dovuto dalla prostatite; altre cause potrebbero essere:

- tensione dei muscoli del pavimento pelvico
- calcoli alla prostata
- stenosi uretrale (restringimento dell'uretra) o tessuto cicatriziale
- tumore alla prostata
- iperplasia prostatica benigna (IPB), ossia un ingrossamento della prostata

COME VIENE DIAGNOSTICATA LA PROSTATITE?

Il medico porrà delle domande per individuare la causa del dolore. Potrebbe eseguire un'esplorazione digito-rettale (EDR) per individuare un ingrossamento o valutarne la dolorabilità o un'ecografia transrettale, o ancora utilizzare un cistoscopio per esaminare più da vicino la prostata. Inoltre, potrebbe essere necessario sottoporsi a esami di laboratorio per rilevare la presenza di batteri nelle urine o nel liquido prostatico, a un'uroflussometria o a un esame urodinamico per individuare un blocco.

TRATTAMENTI

Il trattamento da adottare dipenderà dal tipo di prostatite. È possibile sottoporsi a più trattamenti, fino a quando non si trova una cura efficace.

Antibiotici: spesso utilizzati come prima misura per contrastare i batteri.

Alfa-bloccanti: aiutano a rilassare i muscoli attorno alla prostata e alla base della vescica. Ne esistono di diversi tipi.

Antinfiammatori: farmaci non steroidei per ridurre il dolore tra cui l'aspirina e l'ibuprofene. Contribuiscono anche al rilassamento muscolare.

Massaggio prostatico: aiuta ad alleviare la tensione nella prostata. Viene eseguito drenando il liquido dai dotti prostatici e rilassando i muscoli circostanti.

Biofeedback: un metodo per imparare a rilassare determinati muscoli. Con l'aiuto di un esperto, aiuta a ridurre la tensione del pavimento pelvico.

Rimedi casalinghi: includono bagni caldi, borse di acqua calda e un cuscino a forma di ciambella.

Cambiamenti nello stile di vita: perdere peso e consumare cibi sani, imparare a rilassarsi e fare esercizio fisico per alleviare i sintomi. Non è dimostrato che tisane di erbe e integratori aiutino a curare la prostatite. Si consiglia di consultare il proprio medico per valutare i cambiamenti allo stile di vita da adottare.

Agopuntura: eseguita da un professionista, consiste nel posizionamento di aghi molto sottili nella pelle a diverse profondità e in diversi punti del corpo per aiutare a ridurre il dolore.

Chirurgia: in alcuni rari casi potrebbe essere necessario un intervento chirurgico all'uretra o alla prostata, ad esempio in caso di tessuto cicatriziale uretrale.

DOMANDE DA FARE AL TUO MEDICO

- o Come sa che il mio disturbo è prostatite e non qualcosa di diverso?
- o Il trattamento curerà la prostatite o dovrò convivere per qualche tempo?
- o Quali sono le opzioni di trattamento più adatte al mio caso?
- o Quali sono gli effetti collaterali di ciascun trattamento?
- o Potrò interrompere il trattamento non appena starò meglio?
- o E se il trattamento non dovesse funzionare?
- o Posso continuare ad avere rapporti sessuali?

COSA DOVRESTI SAPERE SULLA PROSTATITE

INFORMAZIONI SULLA FONDAZIONE PER LA CURA UROLOGICA

La Fondazione per la cura urologica è la principale fondazione urologica al mondo e la fondazione ufficiale dell'American Urological Association. Condividiamo informazioni sulla salute urologica per sostenere le persone che desiderano rendere più sana la loro vita. Le nostre informazioni sono basate sulle risorse dell'American Urological Association e sono revisionate da medici specializzati. Per saperne di più, visita il sito web della Fondazione per la cura urologica, **UrologyHealth.org/UrologicConditions** o vai su **UrologyHealth.org/FindAUrologist** per trovare il medico più vicino a te.

DISCLAIMER

Queste informazioni non rappresentano uno strumento di autodiagnosi e non sostituiscono la consulenza di un medico specializzato. Rivolgersi al proprio medico o al proprio urologo per qualsiasi problema di salute.

Chiedere sempre un consulto al proprio medico prima di iniziare o interrompere qualsiasi trattamento, compresi quelli farmacologici. Per altre condizioni urologiche, visitare il sito **UrologyHealth.org/Download** o chiamare il numero 800-828-7866.

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