Original article

Boswellia Gum Resin and Essential Oils: Potential Health Benefits – An Evidence Based Review

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Abstract

Traditional medicine is still widely practiced in many countries due to its complexity and long term benefit. Among various medicinal plants found in Dhofar region of Oman, frankincense has a unique position due to its medicinal and economical importance. The gum-resin and essential oil produced by different species, most of these are related to family *Burseraceae* under the *Boswellia* genus. The family members of *Boswellia* are characterized by resin bearing ducts. Among the twenty-nine species of genus *Boswellia*, (Burseraceae), *Boswellia sacra* Flueck is known since decades for the extraction of aromatic gums and resins that are burned as incense. *Boswellia* resin holds about 60-80% alcohol-soluble resin, 15-20% water soluble gum and 5-7 % essential oil, along with polysaccharide fraction and polymeric substances are also present in limited extent. The physicians and nutritionists show interest in frankincense due to the therapeutic potential of its gum resin and essential oil. Essential oil and gum resin of various species of frankincense has been used to make remedies to treat different diseases. Various reports have described the antimicrobial, immuno-modulatory, anti-inflammatory, hypoglycemic, anticancer, anti-asthmatic, antidiarrheal, hypo-lipidemic, anti-diabetic, hepato-protective, and even antiviral effect of different *Boswellia* species. In this review, we have highlighted the works done so far on the use of *Boswellia* gum resin and health benefits along with some pilot clinical studies done on the *Boswellia* gum resin related products.

Keywords: Boswellia, gum resin, essential oils, health benefits, frankincense

Abbreviations

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

BAs: Boswellic Acids

KBA: Keto Boswellic Acid

AKBA: Acetyl Keto Boswellic Acid

BC: *Boswellia carteri*

TDME: Trans Dermal Micro Emulsion

MEs: Micro Emulsions

5-LOX: 5-lipoxygenase

COX: Cy-clooxygenase

CYP: Cytochrome P450 enzymes

SOD: Superoxide dismutase

MDA: Malondialdehyde

ROS: Reactive Oxygen Species

INF: Interferon

ER/UPR: Endoplasmic Reticulum/Unfolded Protein Response

TNBC: Triple-Negative Breast Cancer

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IKK: Inhibitor of B (IB) kinase

BSE: *Boswellia serrata* extracts

HLE: Human Leukocyte Elastase

LT: leukotrienes

OVA: Ovalbumin

PMNL: Human polymophonuclear leucocytes

DTH: Delayed type hypersensitivity

EMF: Electromagnetic field

RBC: Red blood cells

NF-kB: Nuclear factor kappa B

IA: Incensole acetate

TNF: Tumor necrosis factor

ERK: Extracellular signal regulated kinase

Cys-LT: Cysteinyl leukotriene

UCC: Urothelial cell carcinoma

MS: Multiple sclerosis

BA-PC: Boswellic acid phosphatidylcholine

ABA: Acetyl boswellic acid

IL: Interleukin

IBD: Irritable bowl disease

EAE: Experimental autoimmune encephalomyelitis

Introduction

Medicinal plants are widely used to treat different life threatening ailments. Traditional herbal medicine has not only important role in healing but also contributes to the research on the development of most pharmaceutically important metabolites from plants which are helpful to produce drugs on commercial scale.[1] It is already reported that 90% population of developing countries depend on medicinal plants for primary health care and medicines.[2] Schippmann *et al.* stated that overall worldwide nearly about 50,000 plant species have been used to obtain different types of metabolites for medicinal purposes.[3] Sakkir *et al.* also reported that numerous herbal based drugs systems of treatment were in use to treat the different ailments in the Arabian Peninsula.[4] A number of native plants were used in the past for cosmetic purposes. Most of the native plants are used for bone settings, cupping and cauterization.

Dhofar region of Sultanate of Oman is very rich in plant biodiversity in comparison to other parts of the country. Medicinal and wild plants are available in the hill areas of Dhofar.[5] Among 1206 plant species of Oman, about 800 were recorded in Dhofar region and more than 50 of them are endemic species.[6]

Figure 1: Frankincense tree

Plant profile and geographical distribution of frankincense trees

There are at least 29 members of family *Burserceae*. The plants have medium height neither very short nor tall. The stem is generally covered with thin bark bearing and has compound leaves and star shaped flowers.[7,8] *Boswellia sacra* is a tree aboriginal to region of Dhofar in the Oman. *B. sacra* grow upwards and attains height of five meters. Some plants have several trunks expanding from the base.[7,8]

The frankincense tree (Figure 1) nurtures in the south-western areas of Oman known as Dhofar region and spreads its north-eastern limited area of Hasik. Frankincense is significant wild-growing plants over vast semi-deserted areas, representing a species able to grow on stony hills in a life-threatening and persistent drought ecosystem. It is also found in more humid coastal belt exposed to the south west monsoon and in arid plateaus north of the shoreline hills range of Jabal Al Qara.[9] 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*) as well. The difference in various species of *Boswellia* is based on genetic variation and its segregating among and within populations. The exact knowledge of the species is significant to conserve and breeding of endangered or economically important species.[10,11]

Source of gum resin

The gum-resin formed by numerous classes of tree related to the genus *Boswellia* which is group of plants of resin bearing ducts. Among the twenty-nine species, genus *Boswellia* (*Burseraceae*), *sacra* Flueck is the one recognized since decades to produce aromatic gums and resins that are burned as incense. It is the only inborn species to the Arabian Peninsula, where it is limited to the southwest of

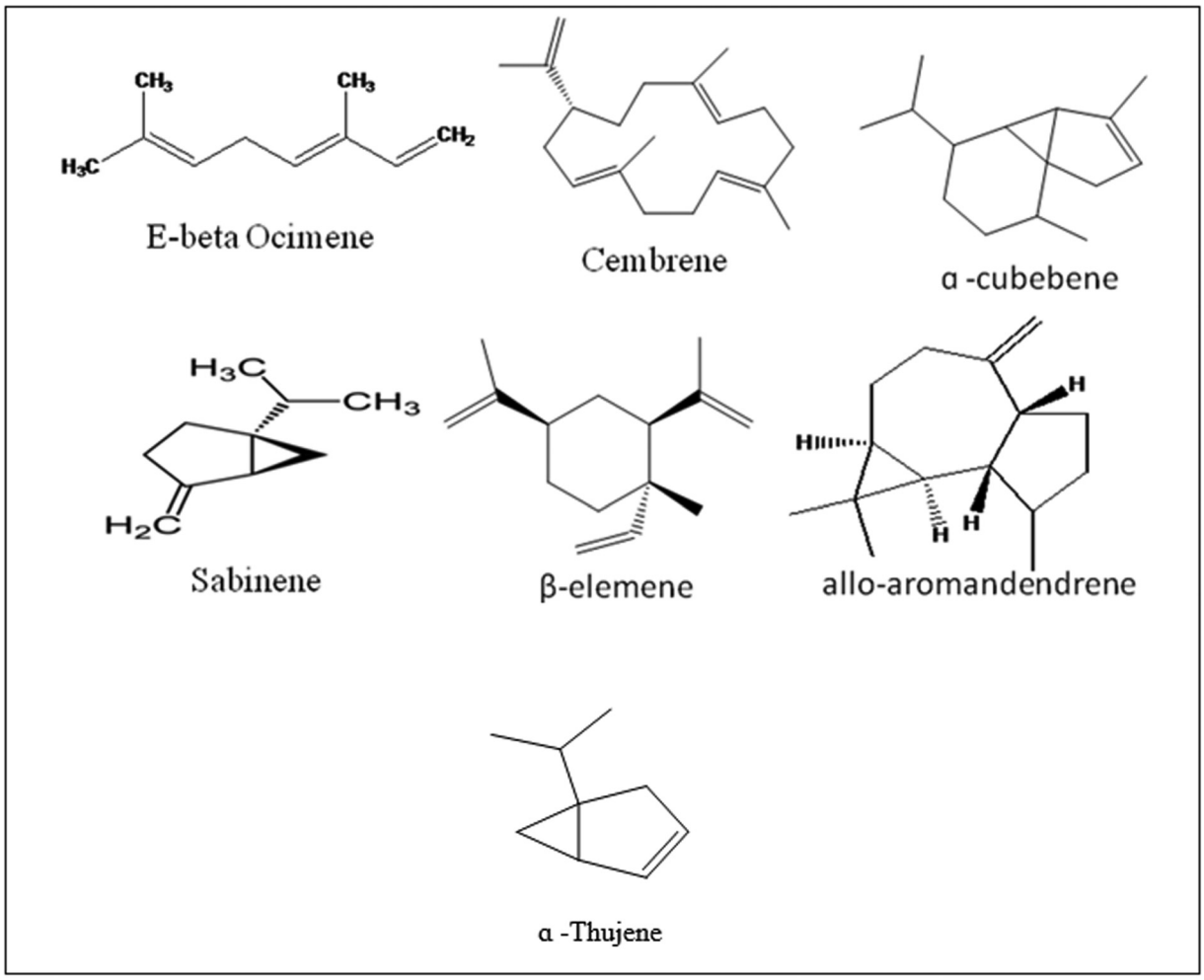

Figure 2: Active phyto-compounds of *Boswellia* species

Oman and the Hadramawt and Mahra regions of Yemen.[9] Besides, Arabia it nurtures also in the Horn region of Somalia, which is today the most imperative center for the manufacture of a gum frankincense recognized as "bejo".[12] The frankincense is prepared from asymmetrical bulges of milky to yellowish brown latex radiated by the stem of the plants and was previously used therapeutically and for delousing by the Egyptians. Since primeval era, Yemen and Oman produced this type of gum, and its trade increased tremendously. According to historical sources, 3,000 tons/year materials like gum and resin related to essence export these nations to transport the countries like Iran and India.[13] *B. sacra* is one of the most significant resources of Oman.[14] Collection of the gum from the stem or bark of frankincense trees has been a significant employment for the people of Dhofar due to its fine quality and market value until the year's last century.[15] Resin or gum of *Boswellia* tree, had been a significant material for export to Arabian Peninsula and North Africa. The price of frankincense gum resin is depending on its quality. High quality and edible variety of frankincense has been sold for $65 per kg and it is significant source of country economy.

Active components of *boswellia* species

Boswellia species resin holds about 60-80% alcohol-soluble resin, 15-20% water soluble gum and 5-7% essential oil, as well as polysaccharides fraction and polymeric substances are also present in limited extent. There are various active phyto-compounds found in *Boswellia* species (Figure 2). The quantity and quality of these compound changes from species to species that makes a species different from each other. The reasons behind these differences are related to climate, harvesting time and geographical condition.[16]

Active ingredients of frankincense gum resin

The chemical composition of frankincense essential oil can be used as a marker to recognized varieties of frankincense. The main constituent of Aden and Omani oil is α-pinene (43%) whereas, Eritrean, Turkish oils are rich in octyl acetate (52%). The Indian frankincense oil is rich in α-thujene (61%).[17] Various active components of gums resin extracts are depicted in Figure 3. Active components shown in Figure 2 such as e-beta ocimene, cembrene, alpha cubebene, sabinene, beta elemene, allo aromandendrene,

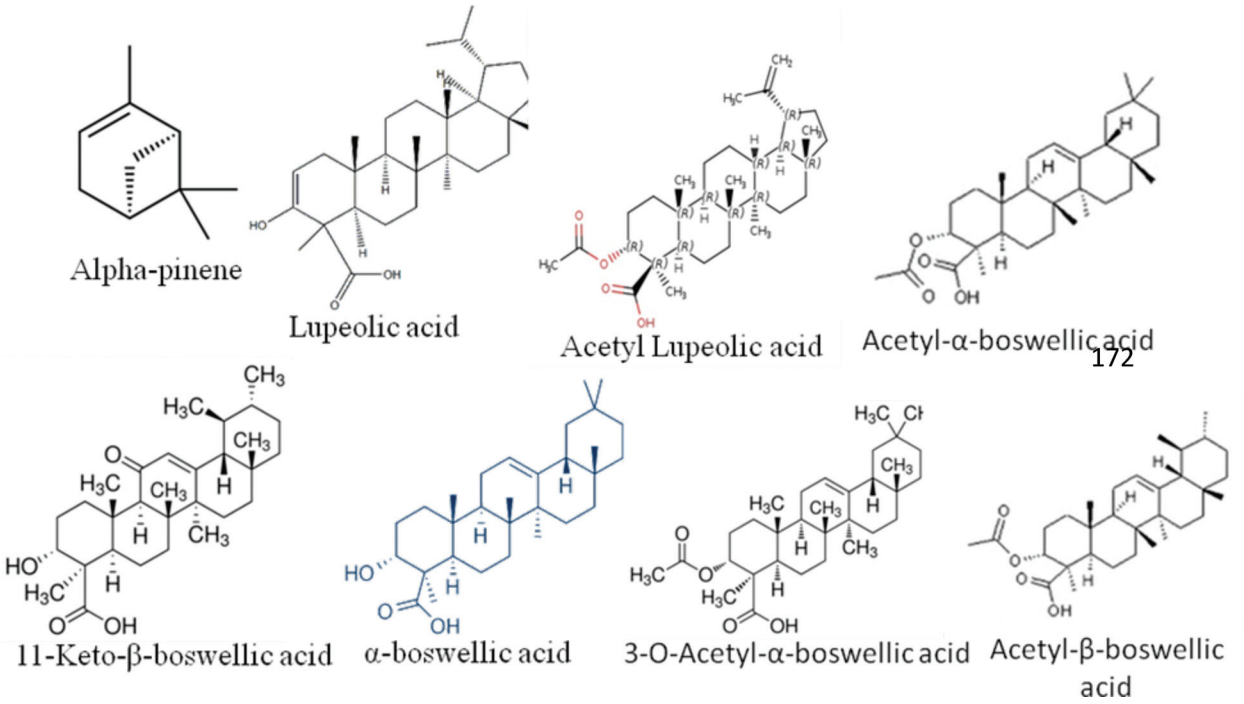

Figure 3: Chemical structures of active component of gum resin

and alpha thujene basically from essential oil. Essential oil extracted from gum resin of *B. sacra* and *B. carterii.* Furthermore alcoholic gums resin extracts both *B. sacra* and *B. carterii* possess rich amount of lupeolic acids and boswellic acids (BA's) (11-keto- beta boswellic acid (KBA), acetyl-11-keto-β boswellic acid (AKBA), alpha boswellic acid, 3-O-acetyl alpha boswellic acid, acetyl beta boswellic acid).

Woolley *et al.* studied the essential oil of *B. carterii* and *B. sacra* and showed that *B. carterii* can always be identified by the key markers viridiflorol, cembrenol, dimethyl ethermorcinol, and most importantly incensole.[18] *B. sacra* was distinguished by higher quantities of α-pinene and delta-3-carene, while *B. carterii* possessed higher quantities of α-thujene, myrcene, limonene, trans-β-caryophyllene, germacrene D, and incensole. Although α-pinene was the major compound and found in high concentrations in all cultivars of Omani frankincense (*B. sacra*) essential oil. Al-Saidi *et al.* reported that this compound cannot be considered as a chemotaxonomic marker for *B. sacra* because of its frequent occurrence in other species of *Boswellia*.[19]

Mono-terpene is a major group (mono-terpene hydrocarbons) that is found in essential oil up to 40%, however, there are some variations exist among species of *Boswellia* on the basis of mono-terpenes concentration.[20] The components of essential oils shows variation from species to species, components such as monoterpene, diterpene, and sesquiterpen are found in most of the oils extracted from various species of *Boswellia*.[20]

Some glycoproteins and proteoglycans have been recognized in frankincense gum resin. Arabino-galactan proteins are the chief constituents of water-soluble polymeric ingredients found in the gum resins of *B. serrata* and *B. carterii*. [21,22] Occurrences of glycoproteins in gum resin were indicated by the presence of high contents of mannose, fructose and glucosamine. The protein fragment is dominated with hydroxy proline and serine. *B. serrata* has higher content of proteins (22%) in the gum in comparison to *B. carterii* (6%).[23] Chevrier *et al.* stated that *B. carterii* and *B. serrata*, besides essential oil and sugars, contains terpenoids and aliphatic octyl acetate accountable for the durable aroma when charred.[24] The gum resin has several additional dynamic components like incensole acetate, incensole, α-boswellic acid and β-boswellic acid, pentacyclic triterpene boswellic acids, 11-keto-β-boswellic acid, acetyl-11dien-β boswellic acid, acetyl-11-keto-β boswellic acid (AKBA), 3-O-acetyl-α-boswellic acid, acetyl-α-boswellic acid and acetyl-β-boswellic acid etc.[25,26,27,28,29]

Impact of human activity on frankincense population

The wild cultivars of frankincense faced various factors related to human activity like cutting of firewood, construction, radiations from telephonic tower etc. Overgrazing in Salalah, Oman is also a critical factor that can affect size of frankincense populations. Various environmental factors like rising temperature and decreasing rainfall can affect various *Boswellia* species population to a critical condition. The decline in the population of frankincense due to the potential harmful ecological and/or economic factors makes the basis of conservation program. In conservation program, the mapping and monitoring has been done to collect the information related to spreading and ecology of various species of frankincense.[9] On the basis of information gathered from conservation program, a reserve area for frankincense has been established known as "Wadi Dowkah Frankincense Park" Dowkah, located about

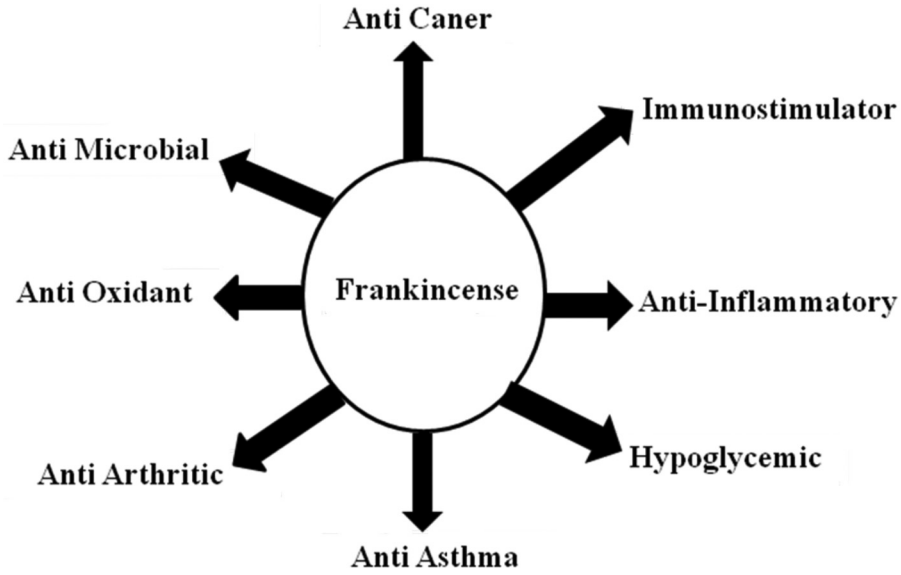

Figure 4: Overall view of medicinal properties of frankincense

Table 1: General active components of *Boswellia* sp. [5]

S. N.	Source	Main components
1.	Gum resin	Incensole, incensyl acetate and verticilla-4(20),7,11-triene, β-amyrin, α-amyrin, β-amyrenone, α-amyrenone, 24-noroleana-3,12-diene and 24-norursa-3,12-diene, lupeolic acid, acetyl lupeolic acid, and boswellic acids (11-keto- beta boswellic acid, alpha boswellic acid, 3-O-Acetyl alpha boswellic acid, acetyl beta boswellic acid, and acetyl-11-keto-β boswellic acid)
2.	Essential oil	n-nonane, tricyclene, α- thujene, α- pinene, camphene, thujadiene, sabinene, β- pinene, β-mircene, n-decane, - 3-carene, P-cymene, limonene, eucalyptole, cis-sabinene hydrate, terpinolene, P-cymenene, linalool, n-undecane, fenchone, α-campholenol, trans-pinocarveol, cis-verbenol, pinocarvone, cis-sabinol, 4-terpineol, p-cymen-8-ol, α-terpineol, n-dodecane, verbenone, trans-carveol, bornyl acetate, thymol, n-tridecane, carvacrol, -elemene, α-copamene, β-bourbonene, β-elemene, n-tetradecane, β-caryophyllene

40 km North of Salalah on Salalah-Thamrit-Muscat Highway. [9]

General therapeutic properties of frankincense and its active constituents

The physicians and nutritionists have interest in frankincense due to the therapeutic qualities of its gum resin and essential oil. It has broad range of medicinal properties which is depicted in Figure 4. Both gum resin and essential oil of various species of *Boswellia* like *B. serrata* and *B. carterii* have been used to make remedy to treat rheumatic and inflammatory diseases[30,31,32], whereas other reports indicated insignificant effect of *B. serrata* in persistent diseases.[33] Furthermore, there are several reports related the use of extracts and essential oils of frankincense gum resin as an antibacterial and antiseptic in a mouthwash as well as in remedy used to treat asthma and coughs.[34] Various studies have described the anticancer, immuno-modulatory, anti-inflammatory, antimicrobial, anti-diabetic and antiviral activities of several *Boswellia*.[35,36,37,38,39]. The active components of *boswellia* and their medicinal properties is depicted in tables 1 and 2.

Therapeutic properties of gum resin

The extract of the gum resin of *B. serrata* gained more popularity in the Western world for the last 2 decades. The usefulness of this extract in the treatment of various inflammatory conditions such as rheumatoid arthritis, asthma, osteoarthritis and inflammatory bowel disease was recognized through *in vitro* assays, animal studies, and pilot clinical trials.[40] In the year 2002, the gum resin extract of *B. serrata* was given the status of Orphan drug by the European Medicine Agency for treatment of peri-tumoral brain edema.[41] In view of their multi facet therapeutic potential as well as nontoxic nature, *Boswellia* species were evaluated for antiulcer activity in different experimental animal models.[42] A study was conducted to formulate and characterize the bioactive fraction of *B. carteri* (BC) loaded trans dermal micro emulsion (TDME) formulations to enhance the bioavailability of biological actives through promoted stratum corneum permeation with the aim of acquiring enhanced and prolonged anti-inflammatory efficacy using low-dose resin loaded MEs and avoiding side effects encountered from high dose and repeated oral administration.[43]

Therapeutic properties of boswellic acids

Early studies suggested that the anti-inflammatory activity of boswellic acids (BA's) is due to interference with the production of leukotrienes, which play a key role in the pathogenesis of inflammation.[44] BAs selectively inhibit

Table 2: Active components of *Boswellia* and their medicinal properties

S.No.	Active components of *Boswellia*	Medicinal Properties
1	E-beta ocimene	Antimicrobial and antioxidant
2	Cembrene	Antimicrobial and antioxidant
3	Alpha Cubebene	Antimicrobial
4	Sabinene	Antimicrobial, antioxidant, antitumor, Larvicidal
5	Beta elemene	Anti cancer, wound healing
6	Allo aromandendrene	Antibacterial, antifungal
7	Alpha Thujene	Antimicrobial and antioxidant
8	Alpha pinene	Anticancer, antidiabetic, antioxidnat, antimicrobial, analgesic
9	Lupeolic acid	Anticancer, anti-inflammatory
10	Acetyl lupeolic acid	Anticancer, antioxidnat, antimicrobial
11	11-keto- beta boswellic acid	Anticancer, antibacterial, anti fungal, anti-inflammatory, Immunostimulator
12	Alpha boswellic acid	Anticancer, antibacterial, anti fungal, anti-inflammatory, Immunostimulator, anti-arthritic
13	3-O-Acetyl alpha boswellic acid	Anticancer, antibacterial, anti fungal, anti-inflammatory, Immunostimulator, anti-arthritic
14	Acetyl beta boswellic acid	Anticancer, antibacterial, anti fungal, anti-inflammatory, Immunostimulator, anti-arthritic
15	acetyl-11-keto-β boswellic acid	Anticancer, antibacterial, anti fungal, anti-inflammatory, Immunostimulator, anti-arthritic, anti asthma

the key enzyme of leukotriene synthesis, 5-lipoxygenase.[45] More recently, it was found that other BAs such as β-BA could also play an important role, targeting the microsomal prostaglandin E2 synthase-1 as well as cathepsin G.[40] Side effects of BAs include abdominal discomfort, nausea, epigastric pain, hyperacidity[46], and diarrhea.[47] Boswellic acid from *B. serrata* belongs to non-steroidal anti-inflammatory drugs (NSAIDs) with a different mechanism of action than those of the common NSAIDs.[48] Several attempts were made to increase the bioavailability of BAs are based on the low systemic absorption of these compounds, especially KBA and AKBA, both in animals and in humans. This fact was confirmed through pharmacokinetic studies.[40] In this context, the beneficial effects of a fatty meal on the bioavailability of BAs combined with the improvement of absorption lately reported for a novel lecithin formulation of curcumin, Meriva[49], have encouraged researchers to compare the bioavailability of BAs in a soy lecithin formulation of the extract of *B. serrata* with the unformulated extract. Husch *et al.* reported a novel data on the tissue distribution of BAs were provided through measurement of the concentration of the six major BAs in plasma as well as in different organs (brain, muscle, eye, liver, and kidney).[44] The lecithin formulation exhibited a significant improvement in the absorption of BAs leading to a promotion in their tissue penetration. These compounds reached concentrations in the range of their anti-inflammatory activity in the organs investigated. This study implies that the organ concentrations achieved match the range required to bring out pharmacological action of BAs, which encourages future testing on humans.[44]

Therapeutic properties of boswellic acid based nano drug formulation

AKBA is the most potent penta-cyclic triterpenic acid present in gum of *B. serrata* for anti-inflammatory and anti-arthritic activity. Topical gel for *in vivo* study of AKBA and AKBA polymeric nanoparticles was formulated by using 1% Carbopol 940. Results of *in vivo* comparison study showed much higher anti-inflammatory activity of AKBA nanogel compared to AKBA gel of equivalent concentration.[50] *B. serrata* was formulated as topical analgesic and anti inflammatory nano emmigel, which is a combination of a nano emulsion and a nano micellar system in a gel base. Improved therapeutic response was obtained as compared to nano emulsion gel, nano-micellar gel, emulgel and also marketed topical product of *B. serrata* when examined for *in vivo* anti-inflammatory and analgesic activity in animal models (Kathpalia et al. 2018).[51] 11-keto-beta-boswellic acid (KBA) was isolated from the oleo-gum resin of *B. serrata*, and its nanoparticle formulation (KBA-NPs) was prepared by the emulsion diffusion evaporation method. Oral bioavailability of KBA and KBA-NP's was studied at 50 mg/kg dose in Sprague Dawley rats, and further evaluated for *in vivo* anti-inflammatory activity in carrageenan-induced rat paw oedema assay at the same dose level. The results of oral bioavailability study and *in vivo* anti-inflammatory activity showed 7- and 1.7-fold increase in bioavailability and anti-inflammatory activity respectively.[52]

Anti bacterial activity of essential oil

The antibacterial effect of essential oil of *B. serrata* was found significant against Gram-positive and Gram-negative bacteria.[53,54,55,35] The essential oil of *B. serrata* inhibited the growth of *Staphylococcus aureus*, *Escherichia coli* and *Proteus mirabilis.* Basar reported antibacterial activity of essential oil of *B. carterii* against *Bacillus*.[21] Further, Basar, 2001 observed that the responsible active components for antibacterial activities were incensole, verticilla-4 (20), 7, 11-triene, AKBA, 3-oxo-tirucallic acid and α- & β-boswellic acid. All above components reported for higher activity in *B. serrata* than that of *B. carterii*.[21] Van *et al.* reported that different fractions of essential oils of *B. carteri*, *B. neglecta*, *B. sacra, B. thurifera*, and *B. frereana*

showed moderate to poor activity against a reference *S. aureus* strain (ATCC 12600).[54] Recently Abdoul-latif *et al.* reported the antibacterial activity of essential oils of *B. sacra* and *B. papyrifera*. Interestingly essential oils of *B. sacra* and *B. papyrifera* present an antimicrobial activity stronger than the tetracycline.[56] Javed *et al.* reported that *B. sacra* oils highest zone of inhibition for *S. aureus* and lowest for the *Klebsiella pneumonia*. [57]

Anti bacterial activity of gum resin

The acid portions of gum resin of *B. carterii* and *B. serrata* are indicated by its effect on bacterial cell. Al-Saidi *et al.* reported antibacterial activity of oleogum resins of *B. sacra*, known as Hoojri, Najdi, Shathari, and Shaabi.[19] The water gum extract of *B. serrata* has clear antibacterial effect on *Proteus vulgaris* indicated by a large zone of inhibition. Other report indicates that 12.5 μg of water extract of *B. serrata* showed prominent anti bacterial effect against *P. vulgaris, E. Coli* and *P. aeruginosa*.[58,59,60,61,62] These findings indicated that antibacterial properties of gum resin may be due to the presence of phenolic in boswellic acid.

Antibacterial activity of boswellic acids

Numerous reports showed that BA's obtained from gum resin of *B. carterii* has antibacterial effect against gram positive bacteria indicated by MIC in the range of 2-8 μg/ml. Moreover, AKβ-BA showed concentration-dependent effect for *S. aureus*.[59] Raja *et al.* (2011) studied antibacterial effect of different boswellic acids obtained from *B. serrata in vitro* condition on oral bacteria and found that AKBA showed highest effect on all bacteria. AKBA worked with in range of 2 to 4 μg/ml of MIC against all tested strains while it showed MIC 12 μg/ml for *Fusobacterium nucleatum*.[59] All the components of gum resin of *Boswellia* species have moderate to higher antibacterial effect on various types of bacteria but AKBA was found to be the most active.

Anti fungal activity of essential oil

Studies indicated that essential oil of various species like *B. carterii*, *B. Serrata, B. papyrifera* and *B. rivae* showed high effect on various fungal strains such as *Malassezia* spp., *Candida albicans* and *Trichophyton spp*.[62,63] Overall the resin and essential oil of *B. sacra* can be recommended as safe plant based preservatives to enhance shelf life of food and food products with reference to adverse effect of physical and synthetic chemical preservatives and their antimicrobial and aflatoxins inhibition activity.

Anti fungal activity of gum resin

B. sacra resin on the growth and aflatoxins production by two species of Aspergilli, namely *Aspergillus flavus* (SQU21) and *Aspergillus parasiticus* (CBS921.7).[64] Resin of *B. sacra* caused 57.9–92.1% inhibition of aflatoxin secretion by *A. flavus* and 43.6–95.7% for *A. parasiticus*. Reports of Camarda *et al.* (2007) indicated gum resin of various species like *B. carterii*, *B. Serrata, B. papyrifera* and *B. rivae* showed high effect on various fungal strains.[62] Vankatesh *et al.* studied *in vitro* and in viable maize the antifungal and antimycotoxigenic effect of essential oil of *B. serrata*.[65] The oil of *B. serrata* found to be antifungal against ground and storage fungi and it inhibit the growth of mycelia at the range between 15.9–56.3% at 1 μL/mL. The values for minimum inhibitory and fungicidal concentrations were in the range of 0.039–0.625 μL mL and 2.5–>10.0 μL mL, respectively. Further Vankatesh *et al.* (2017) observed that the oil of gum resin of *B. serrata* reduced aflatoxin B1 and fumonisin B1 production at 6 μL/mL in vitro condition.[65] Study showed the antifungal effect of gum extract of *B. serrata* on plant pathogenic fungus (red rot disease causing agent) *Colletotrichum falcatum* by agar well diffusion process.[66] These results suggested that these extract can be used to treat diseases caused by the test organism. Our recent finding showed antifungal effect of Najdi crude gum resin against candida and Malassezia furfur (Rashan *et al.* Unpublished).

Anti-inflammatory activity of essential oil

Lee *et al.* studied the anti-inflammatory effects of *B. sacra* essential oil on ovalbumin (OVA)-induced asthma mouse model. BALB/c mice after intraperitoneal OVA sensitization were challenged with intratracheal OVA. These results suggested that inhaled *B. sacra* essential oil as an immune-modulator in Th1/Th2 mediated asthma may have therapeutic potential for the treatment in allergic airway inflammation.[37]

Anti-inflammatory activity of boswellic acids

Several reports indicated that AKBA is the most active inhibitor of 5-LOX, important enzyme to regulate cellular inflammatory. The boswellic acid from *B. carterii* reduced inflammatory mediator's synthesis and restricted the leukotrienes formation by affecting 5-LOX.[32] In this context, Bishnoi *et al.* (2012) clarified that boswellic acid is a non-reducing inhibitor of 5-LOX activity.[67] Boswellic acid inhibit either by direct react with 5-LOX or blocks its translocation. Low production of leukotriene is the main target achieved by boswellic acid by lowering the synthesis of 5-LOX related to anti-inflammation. Additional comprehensive inquiries exhibited boswellic acids as non-redox inhibitors, which might provide site for pentacyclic triterpenes on 5-LOX.[32,68,69] *B. serrata* extract with lower concentration AKBA increased 5-LOX activity.[69] AKBA was recognized as a straight inhibitor of cy-clooxygenase-1 (COX-1), while very little inhabitation was noted in cyclooxygenase (COX-2) was only inhibited by boswellic acids.[70] The inhibition of 5- LOX, due to presence of boswellic acids, can inhibit synthesis of leukotriene in neutrophilic granulocytes. Boswellic acids also showed inhibition of prostaglandin, 12 lipooxynebase, cytokines and p-glycoprotein.

Antioxidant potential of gum resin

There are some reports available in the literature indicated antioxidative effect of gum resin of *Bo-swellia* species. Pharmacokinetic studies of secondary metabolites of various *Boswellia* species have shown that components present in gum resins are potent inhibitors of Cytochrome P450 (CYP P450) enzymes. Components of gum resin also have the potential to inhibit the main drug metabolizing enzymes.[71] Hartman *et al.* reported that limonene and esters present in the gum resin are responsible for antioxidant activity.[71] Chilelli *et al.* studied effect of supply of *Boswellia serrata* gum resin and curcumin on plasma levels of markers of oxidative stress, glycation, and inflammation in cyclists.[72] They found that positive effect of supplementation of curcumin and *B. serrata* gum resin glycol-oxidation and lipid peroxidation. Gum resin extract of *B. serrata* were tested for their effect on intestinal inflammation on colonic epithelial cells treated with hydrogen peroxide or INF-γ+TNF-α induced *in vitro* model of intestinal inflammation.[73] Kivrak *et al.* studied the effects of 900-MHz radiation on the hippocampus and cerebellum of adult rats and attenuation of such effects by folic acid and *B. sacra* gum extract. [74] Kivrak *et al.* also investigated the neuroprotective effects of the antioxidants of *B. sacra* and folic acid against exposure to electromagnetic field (EMF).[74] The reports indicate that EMF caused a significant decrease in total pyramidal and granular cell numbers in the hippocampus, dentate gyrus (DG) and in Purkinje cell numbers in the cerebellumin the EMF group compared to the other groups. BS and FA attenuated the neurodegenerative effects of EMF in the hippocampus and cerebellum.

Antioxidant potential of boswellic acids

Ebrahimpour *et al.* studied the neuroprotective effect of Boswellic acid and noted that antioxidant activity of boswellic acid increase capability of cognitive function in a rat model.[75] Beghelli *et al.* showed that the antioxidant power and phenolic content was noted in AKBA concentration.[76] Chen *et al.* observed that AKBA significantly augmented activity of the antioxidant enzyme SOD and also reduced MDA and ROS.[77] Ebrahimpour et *al.* suggested that the effect of boswellic acid from *B. carteri* in improving the cognitive function may be mediated through its antioxidant activity.[75]

Effect of gum resin on immunity

Sharma *et al.* noted that alcoholic extract of *B. serrata* resin has effect on immune responses related to cellular and humoral of mice and leucocyte movement in rats.[30] Data indicated that oral supply of extract of *B. serrata* gum resin reduced the production of antibody as well as cellular responses to sheep RBCs of mice. *B. serrata* and its ingredients including boswellic acids have an effect on the immune system in diverse manners. [16] Chevrier *et al.* reported that extract of *B. carterii* has significant effect on TH-2 cytokines production by murine splenocytes.[24] Khajuria *et al.* confirmed that oral dose in the range of 1–10 mg/kg of a polymeric fraction (BOS 2000) from *B. serrata* improved the levels of IFN-α, TNF-α- and IL-4, in the serum.[78] *B. serrata* extracts may decline the cellular activity related to immune system by suppression of activation, differentiation of B and T lymphocytes and proliferation, tissue destruction, action of NK cells, antibody production and fever.[79] Moussaieff *et al.* demonstrated that the major NF-kB inhibitory components in *B. carteri* resin are incensole acetate (IA) and its non acetylated form incensole (IA) and they concluded that IA and IkB kinase and not boswellic acids inhibited IkB alpha degradation.[80] TAK1 plays a critical role in TNF-induced NF-kB activation.[81] TAB2 and TAB3 are adaptors that link the kinase TAK1 to upstream regulators in the proinflammatory TNF signaling pathway. [82]

Effect of boswellic acid on immunity

Syrovets *et al.* described that ABA and AKBA repressed TNF α in dose range between 1 and 10 μM in human monocytes stimulated by lipopolysaccharide. The effect was arbitrated by direct suppression of IKB-α-kinases carried inhibition of NFB and consequent downregulated the TNF-α- expression in human monocytes. [83]

Anticancer activity of frankincense essential oil

Noticeably essential oil extracted by hydrodistillation method was recognized to be an effective anti-proliferation agent against breast cancer (MDAMB-231 and MCF-cells).[39] Further, Suhail *et al.* demonstrated that *B. sacra* essential oil suppressed protein kinase B and extracellular signal regulated kinase (ERK1/2) expression in human breast cancer cell lines.[39]

Anticancer activity of frankincense gum resin

Xia *et al.* (2017) observed that hydro-distillate of gum resin of *B. sacra* have chemo-preventive activity against invasive urothelial cell carcinoma.[84] The extracts from *Boswellia* species gum have anti-cancer activities, the fact is based on data obtained from experiments to find out their pro-apoptotic activities and anti-proliferative in human leukemia cell lines[85], including their anti-carcinogenic activity in chemically tempted mouse skin cancer models.[86] Ranjbarnejad *et al.* (2017) noted that gum resin extract of *B. serrata* suppressed multiplication, migration and angiogenesis. Extract induced apoptosis in HT-29 through suppressing the mPGES-1 and reducing the PGE2 level and its targets.[87] Extract of gum resin of *B. serrata* reduced level of protein in enzymes related to inflammatory like cyclooxygenase-2 and inducible nitric oxide synthase in mucosa of colon. Koeberle *et al.* (2018) recognized lupeolic acid in gum resins of *Boswellia* species able to inhibit cytosolic phospholipase A2α responsible for inflammatory response.[88] Ahmed *et al.* (2015) conducted an experiment to recognize *in vitro* anticancer effect of

extracts of *B. serrata* bioactive ingredients on HCT 116 and HepG2 cell lines.[89] Sharma *et al.* (2004) exposed broad kinetics of BAs after oral application of gum resin extract of various *Boswellia* species and established relation between food intake and pharmacokinetic of BAs.[90]

The ethanolic extract of *B. serrata* gum resin has showed its cytostatic and apoptosis inducing effect in LN-18 and LN-229 brain tumor cells.[85] A variety of purified tri-terpenoids from frankincense oleo gum resin have been tested preclinicallly as apoptosis inducing, antitumor agents, for example in treatment resistant prostate cancer.[83,91,92,93]

Anticancer activity of frankincense derived active compounds

Recent review states that potential anti cancer activity of boswellic acid active compound from frankincense.[94] Plasma availability of nano particle encapsulated with 11-keto-β-boswellic acid (KBA) was studies and it was shown that KBA can retain in the plasma for longer time and it implicates its bioavailability in the system.[53] Frankincense active compound acetyl keto boswellic acid (AKBA) has been shown to inhibit proliferation and elicit cell death in chemoresistant androgen-independent prostate cancer cells (PC-3) *in vitro* and *in vivo*. AKBA can also inhibit constitutively active NF-B signaling by intercepting the Ikappa B kinase (IKK) activity.[83] Boswellic acids and alcohol soluble ingredients of *Boswellia* species shows apoptotic and cytostatic effect in multiple cancer cell lines of human like fibrosarcoma, malignance, meningioma, leukemia and colon cancer.[95] The anti-cancer influence of Boswellic acid has impact on the endoplasmic reticulum/ unfolded protein response (ER/UPR response) involved in counter to multiple targets of progress, propagation and metastasis of triple-negative breast cancer (TNBC) cancer cells.[96] Boswellic acid inhibited leukocyte elastase.[48] The triterpenoid acetyl-lupeolic acid obtained from *B. carterii* gum resin decreased the cancer cell viability more competently than lupeol. AKBA suppresses docetaxel-resistant prostate cancer cells *in vitro* and *in vivo* by blocking Akt and Stat3 signaling.[97] Moreover, direct anti-proliferative/pro-apoptotic property of boswellic acid was tested on leukemia cell lines and report indicates that significant effect due to activation of caspase-3/8/9 by boswellic acid. [98] In leukemia, the antitumor activity of four major triterpene acids including beta-boswellic acid, 3-O-acetyl-beta-boswellic acid, KBA, and AKBA isolated from the gum resin of *B. serrata* was examined, and it was found that in HL-60 human leukemia cells, there was a dose dependent inhibition of the synthesis of DNA, RNA, and protein.[99] Boswellic acid acetate, a compound found in the herb *B. carteri* Birdw, could induce differentiation and apoptosis of leukemia cells, HL-60, U937, ML-1 cells, NB4, SKNO-1, K562, and U937 cells.[100,101] Liu *et al.* (2006) demonstrated that AKBA inhibited cellular growth in several colon cancer cell lines. [102] Further, Liu *et al.* (2006) showed that the growth inhibitory effect of AKBA was dependent on P21 but not P53 suggesting that P21 may have protected cells against apoptosis by inducing a G1 arrest.[102] Lu *et al.* (2008) suggested that AKBA induces apoptosis in prostate cancer cells through a death receptor 5 (DR5-mediated pathway), which probably involves the induced expression of CCAAT/ enhancer binding protein homologous protein (CHOP).[103] Pang *et al.* (2009) found that AKBA suppress VEGF receptor 2 (VEGFR2) kinase (KDR/ FIK-1) with an IC_{50} value of 1.68 μmol/L. Further, they also demonstrated that AKBA suppressed the downstream protein kinases of VEGFR2, including Src family kinase, ERK, AKT, mTOR and ribosomal protein 56 kinase, suggesting that AKBA potentially inhibit human prostate tumor growth through inhibition of angiogenesis induced by VEGFR2 signalling pathway.[104] Park *et al.* (2011) reported that AKBA can suppress the growth and metastasis of human pancreatic tumors in an orthotopic nude mouse model that correlates with modulation of multiple targets.[105] The pentacyclic triterpenoids of *B. serrata* has ability to reduce the development of cancer in prostate cell.[106]

The cytotoxic and antitumor properties are mostly due to stimulation of apoptosis by AKBA and its ability to activate caspase, NF-B down regulation, improved Bax expression.[107] Syrovets *et al.* (2005) reported that acetyl boswellic acid (ABA) can inhibit topoisomerases I and IIα through struggle with DNA for enzyme binding. [83] In another study Syrovets *et al.* noticed that ABA and AKBA reduced the activities of human recombinant His-IKKβ and GST-IKKα. [83] These results indicated that molecular properties of ABA and AKBA containing treatments for the anti-inflammatory and recommended that ABA may be used as template to develop new therapeutic drugs. Hoernlein *et al.* (1999) studied property of AKBA and noted that AKBA inhibited 5- LOX.[108] Further, they observed that AKBA induced apoptosis by inhibiting topoisomerase I in CCRF-CEM and HL-60 cells. Syrovets *et al.* (2005) observed that AKBA and linked molecules work on IKK might offer a novel method for the treatment of chemo-resistant human tumors such as androgen-independent human prostate cancers.[83] BA, especially AKBA, BBA, and ABA, has been shown to exert marked cytotoxicity on malignant glioma cells even at lower micromolar concentrations, primarily through apoptosis induction, and it is independent of free radical formation. BA induced the expression of p21, which is not reliant on the p53 pathway, without altering the levels of BAX and BCL-2 proteins.[109] Xue *et al.* (2016) studied the reversal of multidrug-resistant (MDR) by AKBA in a human ileocecal adenocarcinoma cell line with vincristine (VCR)-induced resistance, HCT-8/VCR.[110] They found that AKBA had a maximum "fold reversal' of MDR of 9.19 fold. Further, Xue *et al.* (2016) also observed that the HCT-8 cells treated with AKBA and VCR exhibited a higher percentage of apoptotic tumor cells using flow cytometry. On the other hand, they

also reported that AKBA inhibited the expression of P-gp (p-glycoprotein) and decreased levels of expression of MDR gene 1 in HCT-8/VCR cells and they concluded that AKBA might be a potential agent to reverse MDR in human ileocecal adenocarcinoma.[110] On the other hand, Toden *et al.* (2015) investigated the antitumorigenic effects of curcumin and AKBA on modulation of specific cancer-related miRNA in colorectal cancer cells and validated their protection effects *in vivo* using a xenograft mouse model.[111] Toden *et al.* (2015) discovered that curcumin and AKBA induced upregulation of tumor-suppressive miR-34a and downregulation of miR-27 in a colorectal cancer cells.[111] Further, Pasta *et al.* (2016) demonstrated in a mouse xenograft model that both curcumin and AKBA treatments suppressed tumor growth. Pasta *et al.* conducted a pilot study to treat pain of breast cancer patients with the combination of boswellic acid, betaine, and myo-inositol.[112]

Frankincense as radiation protection agent

Togni *et al.* tested the efficacy and safety of the application of a *boswellia* based cream during adjuvant radiotherapy of patients with breast carcinoma.[113] The treatment was well tolerated and no severe adverse effects were observed in the study population. As a primary endpoint they examined the intensity of the erythema upon radiotherapy at 50 Gy in the patients who received daily applications of *boswellia* species cream compared with those who received the base cream as placebo. The intensity of erythema was evaluated by using a visual grading scale11 and by a more objective computer-assisted analysis of the digitalization of the skin color associated to advanced stages of erythema, as a measure of the intensity of the process. The results of the two approaches were partially consistent. The analysis with the non-parametric Mann-Withney test on the skin color difference ("delta magenta" test) revealed a statistically significant increase in efficacy of the use of *boswellia* cream compared with placebo. Moreover, the χ-square analysis of the data obtained with the visual intensity method revealed a significant difference between the two groups, suggesting a positive effect of the *boswellia* cream in reducing the intensity of the erythema (higher number of patients who scored slight erythema). The efficacy of the treatment with *boswellia* cream was further confirmed by the analysis of data on patients who were treated with concomitant chemotherapy. The use of topical corticosteroids in the control of radiation-induced dermatitis has been proposed for decades with debated efficacy. They aimed at verifying whether the use of *boswellia* cream could reduce the use of topical cortisone by patients undergoing radiotherapy. The results clearly indicate that a statistically significant lower percentage of patients receiving *boswellia* cream make use of topical corticosteroids, compared to those receiving the base cream. According to the toxicity defined by RTOG criteria 14 a difference "close to significant" was observed for degree 1 and 2 between the patients of the two groups. In fact, a trend of a lower incidence of skin superficial symptoms (itching, burning sensation) was observed in the *boswellia* cream group, suggesting that patients receiving boswellia cream may experience a reduced superficial toxicity in comparison with patients receiving placebo.

Frankincense oleo gum resin contains plethora of compounds which certainly deserve further exploration as valuable and selective antitumor compound. *B. sacra* essential oil induces breast cancer cell-specific cyto-toxicity. Suppression of cellular network formation and disruption of spheroid development of breast cancer cells by *B. sacra* essential oil suggest that the essential oil may be effective for advanced breast cancer. Consistently, the essential oil represses signaling pathways and cell cycle regulators that have been proposed as therapeutic targets for breast cancer. Further clinical studies on the efficacy of *boswellia* clearly states that it can alleviate pathogenesis related manifestation in cancer patients and as a topical agent it can reduce severity of erythma in patients who undergo radiotherapy. However, it is strongly suggested to study the molecular mechanism of *boswellia* derived active principles in respective clinical models.

Anti-arthritic activity of gum resin

Fan *et al.* reported that an acetone extract of gum resin of *B. carterii* decreased arthritic scores, reduced paw oedema and significantly suppressed local tissue TNF-α- and IL-1β in rats.[114] Chimenti *et al.* (2015) obtained an association between bone homeostasis and in-flammation in rheumatoid arthri-tis related to cytokines like TNF-α, IFN-α-, IL-1β and IL-6 expressed in patients with retinoid acid and also in the arthritic joints of rats with collagen stimulated arthritis, while both IL-4, and IL- 10 suppressed cartilage and bone pathology in retinoid acid.[115] Park and Hong, (2016) indicated that NF-kB regulated the many genes that induced IL-1β, TNF-α, IL-6, COX-2 and iNOS, responsible for the proteins synthesis in inflammation.[116] It was validated that triterpene acids blocked inflammatory reactions in both acute and chronic inflammation models.[117] Curcumin is combined with *B. serrata* to enhance its anti-inflammatory effect, especially since a number of pivotal enzymes involved in inflammation, like 5-LOX, cathepsin G, and microsomal prostaglandin E synthase – 1 as well as NF-B and several pro-inflammatory cytokines like TNFα, IL-1β, interleukin-2 (IL-2), and IL-6 are also inhibited by boswellic acids, which have been shown to inhibit inflammatory mediators in experimentally induced arthritis.[118]

Anti-arthritic activity of boswellic acids

Derivatives of boswellic acid have been demonstrated to suppress IL-β induced apoptosis of chondrocytes as well as TNF-α induced production of MMP3 by synovial fibroblasts thus demonstrating clear therapeutic potential for the treatment of osteoarthritis.[119] 80% of the population has radiographic evidence of osteoarthritis by age 65, and over 60% of those have symptoms of osteoarthritis.[120]

Analgesic and psychopharmacological property of frankincense

Frankincense is used to treat muscular and arthritic pain in several traditional system of medicine.[121,122] There are several other remedies made from frankincense used in Oman including "Luban Dhakar" which is used for treatment of cold, cough and fever. This is probably due to the analgesic effects of frankincense.[123]

Anti analgesic activity of essential oil

Al-Harrasi *et al.* studied analgesic effects of crude extracts of *B. sacra* on animal models.[123] Further Al-Harrasi *et al.* reported that the most significant inhibition was produced by Shabi frankincense oil (57.5% in early phase, and 55.6% in late phase).[123] In addition, the extracts showed comparable percentage of inhibition to the oil and found in the following order: 60% chloroform/n-hexane sub-fraction (55.3% in early phase, and 66.7% in late phase), and 70% chloroform/n-hexane sub-fraction (59.6% in early phase, and 63.0% in late phase).

Anti analgesic activity of gum resin

Sharma *et al.* reported the anti-inflammatory and analgesic activity of gum resin extract and the sub-fractions of *B. serrata* [122] They conducted formalin test on all the test samples to confirm and support the possible analgesic mechanism for the tested samples of *B. sacra*. The results of the formalin test indicated that tested samples showed significant anti-nociceptive effects in both the early and the late phases. This inhibition in both the early and the late phases of formalin induced pain test indicated the contribution of both mechanisms in the overall analgesic effect. Menon and Kar found that the *B. serrata* extract (BSE) possess marked analgesic activity along with sedative effect.[124] They also observed significant reduction in the spontaneous motor activity after treatment with *B. serrata*. Moussaieff *et al.* observed that ex-tract from *B. carterii* contains an IA, repressed interleukin (IL)-1β synthesis.[125] We also observed anti-inflammatory and analgesic activity of gum resin of *B. sacra* compared with standard drugs (Rashan *et al.* Unpublished).

Anti analgesic activity of boswellic acids

Bishnoi *et al.* investigated the analgesic activity of AKBA at different dose levels by acetic acid induced writhing method and tail flick method in mice.[67] They observed a dose dependent increase in antinociceptive activity of AKBA in acetic induced writhing while in tail flick method 100 mg of AKBA exhibited similar response to 200 mg. AKBA was revealed to be better than positive control, nimesulide.[67]

Efficacy of gum resin on leukocyte migration

The BSE has an effect on production of antibodies and cell-mediated immunity and it also inhibits human leukocyte elastase (HLE).[48] This could be of help in autoimmune disorders like rheumatoid arthritis. Studies in animal models showed that the ingestion of a defatted alcoholic extract of *B. serrata* decreased polymorphonuclear leukocyte infiltration and migration as well as primary antibody synthesis and led to almost total inhibition of the classical complement pathway.[30] Mixed acetyl boswellic acids, pentacyclic triterpenes extracted from the gum resin of *B. serrata* Roxb., significantly inhibited the ionophore-stimulated release of the leukotrienes (LT) B4 and C4 from intact human polymorphonuclear neutrophil leukocytes (PMNLs), with IC_{50} values of 8.48 μg/ml and 8.43 μg/ml, respectively.

Efficacy of boswellic acids on leukocyte migration

Unlike other pentacyclic triterpenes, boswellic acid inhibits the leukocyte elastase with a half maximal inhibitory concentration of 15 μM.[48] Its anti-inflammatory properties were proved by inhibiting 5- LOX, human leukocyte elastase and the NF-kB pathway, without exerting the adverse effects known for steroids.[70] The reduction in the paw edema and lysosomal enzyme activities after boswellic acid treatment suggests that its anti-inflammatory effect was associated with significant reduction of total leukocytes migration as well as lymphocytes and monocytes/macrophages migration from the blood into the synovial cavity. It has been well established that boswellic acids acts as a leukotriene LTB4 inhibitor and reduces the infiltration of leucocytes into an inflammation site.[42] Noticeably, the comparative agent MK 886 (3-[1-(4-chlorobenzyl)-3-t-butyl-thio-5-isopropylindol-2-yl]-2,2-dimethylpropanoic acid, L-663,536, CAS 118, 414-82-7) was about 10 to 100-fold more active than the boswellic acids in inhibiting the formation of 5-LOX products in human polymorphonuclear leucocytes (PMNLs), with IC_{50} values of 0.0068 μg/ml (LTB4) and 0.49 μg/ml (LTC4). After daily intraperitoneal dosage the extract of mixed ABA (20 mg/kg) significantly reduced the clinical symptoms in guinea pigs with experimental autoimmune encephalomyelitis (EAE) between days 11 and 21. However, the inflammatory infiltrates in the brain and the spinal cord were not significantly less extensive in the treated animals than in the respective control group. The multiple intraperitoneal applications of boswellic acids did not inhibit the ionophore-challenged *ex vivo* release of leukotrienes B4 and C4 from PMNLs separated from the blood of guinea pigs with EAE. The boswellic acids have thus been characterized as selective, non-redox and potent inhibitors of the biosynthesis of LT's *in vitro*.[31] 11-KBA activate p38 MAPK and p42/44MAPK and stimulate Ca^{2+} mobilisation in PMNL. BAs act via Gi/0 protein(s) stimulating signalling pathways that control functional leucocyte responses, in a similar way as chemoattractants, i.e. N-formyl-methionyl-leucyl-phenylalanine or platelet-activating factor. Chemo-attractants elicit various functional responses of different leucocytes involving Ca^{2+} mobilisation and activation of MAPK.[126,127]

Hypoglycemic effect of frankincense

Diabetes is a metabolic disorder resulting from insulin resistance or occurring impaired insulin secretion, therefore a diabetic patient will suffer from chronic hyperglycemia.[128] Chronic high blood glucose in diabetes leads in advanced glycation end-products which will subsequently produce reactive oxygen species (ROS). The free radicals originating from damaged cell membranes and lipid peroxidation, causes irreversible damage to the liver, kidneys, eyes, nervous system, cardiovascular and other parts of the body.[129] Oxidative stress as one of the mechanisms in diabetes mellitus, from which carbohydrate metabolism, lipids and proteins are affected, diabetes is characterized by increase oxidative stress and hyperglycemia was shown to directly induce oxidative stress by depleting natural anti-oxidants and facilitating the production of ROS under diabetic conditions.

Hypoglycemic effect of gum Resin

Studies showed that BSE could reduce blood sugar and HbA1c level in diabetic rats.[130] BSE at the dose of 200 mg/kg showed the highest effect compared with other doses.[130] Microscopic slides of the liver and kidney tissues demonstrate that BSE has anti-oxidant and anti-hyperglycemia effects. BSE in doses of 200, and 400 mg/kg can largely reduce the harmful effects of diabetes, that including lymphocytic inflammation in the port areas, irregularities, apoptosis of liver cells, and dilatation of the sinuosoids were not observed. BSE at the dose of 600 mg/ml did not show a protective effect on liver and also cause cell death, inflammation and vasodilatation in sinuosoids space.[130]

Anti-diarrheal effect of gum resin

Borrelli *et al.* evaluated the effect of a BSE on intestinal motility and diarrhoea in rodents.[131] They demonstrated that BSE inhibited upper gastrointestinal transit in croton oil-treated mice as well as castor oil-induced diarrhea but did not affect intestinal motility in control mice, both in the small and in the large intestine. BSE prevents diarrhoea and normalizes intestinal motility in pathophysiological states without slowing the rate of transit in control animals. These results could explain, at least in part, the clinical efficacy of this remedy in reducing diarrhoea in patients with inflammatory bowel disease. Clinically established symptomatic improvement of inflammatory bowel disease symptoms (including the reduction of the diarrhoea) seen under treatment with *B. serrata* and its traditional use in ayurvedic medicine as an anti diarrhoeal agent. On the other hand, studies of effect of BSE on caster-oil induced diarrhea in experimental animals concludes that BSE can normalize the intestinal mobility altered by an inflammatory stimulus and possesses antidiarrheal activity.[132]

Immunomodulatory effect of boswellic acids

Boswellic acids, a mixture of pentacyclic triterpene acids (BA) obtained from *Boswellia serrata* Roxb., have been investigated for their effect on cell mediated and humoral components of the immune system and the immune toxicological potential. A single oral administration of BA (50–200 mg/kg) inhibited the expression of the 24 h delayed type hypersensitivity (DTH) reaction and primary humoral response to SRBC in mice. The secondary response was appreciably enhanced at lower doses. In a multiple oral dose schedule BA (25, 50 and 100 mg/kg) reduced the development of the 24 h DTH reaction and complement fixing antibody titres and slightly enhanced the humoral antibody synthesis. In concentrations greater than 3.9 μg/ml BA produced almost similar and dose related inhibition of proliferative responsiveness of splenocytes to mitogens and alloantigen. Pre-incubation of macrophages with different concentrations of BA enhanced the phagocytic function of adherent macrophages. Prolonged oral administration of BA (25–100 mg/kg/d×21 days) increased the body weight, total leukocyte counts and humoral antibody titres in rats. It is not cytotoxic nor does it cause immunosuppression.[133]

Immunomodulatory effect of gum resin

BSE containing 60% acetyl 11-KBA along with other constituents such as 11-keto β- boswellic acid, AKBA and β- boswellic acid has been evaluated for antianaphylactic and mast cell stabilizing activity using passive paw anaphylaxis and compound 48/80 induced degranulation of mast cell methods. The extract inhibited the passive paw anaphylaxis reaction in rats in dose-dependent manner (20, 40 and 80 mg/kg, po). However, the standard dexamethasone (0.27 mg/kg orally) revealed maximum inhibition of edema as compared to the extract. A significant inhibition in the compound 48/80 induced degranulation of mast cells in dose-dependent manner (20, 40 and 80 mg/kg orally) was observed thus showing mast cell stabilizing activity. The standard disodium cromoglycate (50 mg/kg, ip) was found to demonstrate maximum per cent protection against degranulation as compared to the extract containing 60% AKBA. The results suggest promising anti anaphylactic and mast cell stabilizing activity of the extract. The total alcoholic extract of oleogum resin and the volatile oil have shown a significant immunostimulant action on T-lymphocytes (90% lymphocyte proliferation) that is comparable to the standard immunostimulants viz. *Echinaceae purpurea* extract and (S)-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-b] thiazole hydrochloride (levamisole). The individual components of the resin elicited mild to moderate immunostimulant activity. It is advisable to use the total extract of the oleogum resin in herbal preparations intended for immunostimulation.[28] Mikhaeil *et al.* reported the essential oil of *Boswellia* species exhibited a strong immunostimulant activity (90% lymphocyte transformation) when assessed by a lymphocyte proliferation assay.[28]

Hypolipidemic effect of boswellic acid

Hypolipidemic activity of boswellic acids and its complexation with phosphotidylcholine of *B. serrata* in ex-

vivo in experimental rats has been reported.[32] Iram *et al.* demonstrated that boswellic acid- phosphatidylcholine (BA-PC) complex has significantly increased absorption through the intestine of rats compared with boswellic acid. Further, the (BA-PC) complex showed better anti-inflammatory and hypolipidemic activity as compared with boswellic acid.[32]

Hypolipidemic effect of gum resin

Pandey *et al.* found that the water extract of *B. serrata* possesses strong hypocholestrolemic property along with the increase in serum HDL.[134] It inhibits the lipopolysaccharides induced nitric oxide production by the activated rat peritoneal macrophages and further it showed hepato-protective of reno-protective property. Jaafaru *et al.* studied the hyperlipidemic potential of methanol extract of *B. dalzielli* hutch stem bark extract in rats.[135] They revealed that the stem bark extract showed hypolipidemic and cardio protective properties in triton X-induced hyperlipidemic rats. The efficiency of long-term consumption of *B. serrata* on glycaemic and lipid profiles in patients with type 2 diabetes. This study indicates that supplementation of *B. serrata* in three 300 mg doses daily for 6 weeks, significantly improves HDL, LDL and total cholesterol level and serum SGPT, SGOT in type 2 diabetic patients.[136]

Effect of frankincense gum resin on IBD

The initial clinical studies suggested that *B. serrata* resin could be effective in IBD. In 2002, the European Medicines Agency categorized *B. serrata* gum resin extract in the category of "orphan drugs". *B. serrata* gum resin extracts could influence the immune system in many ways. *B. serrata* represses the formation of leukotriene *via* inhibition of 5-LOX with the action of two boswellic acids, namely 11-KBA and AKBA.[40] The gum resin of *B. serrata* has been shown to be an effective in the treatment of chronic colitis, with a few side effects.[137] Hartmann *et al.* evaluated the anti-inflammatory and antioxidant effects of BSE administered orally (34.2 mg/kg/day) in experimental rat model of acute ulcerative colitis induced by the administration of 4 ml of 4% acetic acid (AA).[71] The study proved that the BSE inhibits inflammatory mediators in acute experimental colitis is rodents and that leads to its protective anti-inflammatory and antioxidant effects. *B. sacra* water extract (5 ml/kg, p. o) aggravated acetic acid-induced chronic ulcers, wherein an increase in ulcer index and ulcer score was observed. In pylorus-ligated rats, the extract increased gastric content volume, free acidity, total acidity, ulcer index, and pepsin activity. There was no significant effect on the development of ethanol-induced and aspirin-induced ulcers while an increase in the development of stress-induced ulcers was observed. The extract did not produce any ulcers when administered to normal rats. The dose of 2 ml/kg was less proulcerogenic compared with 5 ml/kg. The GC-MS analysis revealed the presence of several phyto-constituents that included menthol, 3-cyclohexen-1-ol, and octanoic acid. *B. sacra* water extract has pro-ulcerogenic activity due to its gastric hypersecretory effect.[138] *B. sacra* water extract aggravated the acetic acid-induced gastric ulcers compared with vehicle-treated control. The proulcerogenic effect of *B. sacra* water extract was due to augmented secretion of gastric acid and pepsin, as demonstrated in pylorus-ligated rats. There was no effect on gastric cytoprotection in ethanol-induced gastric ulcers and aspirin-induced gastric ulcers. The aggravation of stress-induced gastric ulcers could also be due to the gastric hypersecretory effect of BSE.

Effect of boswellic acid on asthma

Liu *et al.* investigated the effect of boswellic acid on airway hyper responsiveness, inflammatory cell infiltration, Th2 cytokine and OVA-specific IgE production in a mouse model of asthma.[139] Data showed that Boswellic acid treated groups suppressed allergic airway inflammation, AHR, OVA-specific IgE and Th2 cytokines secretion. It also suppressed the expression of pSTAT6 and GATA3 in a dose dependent manner. Reports suggested that mechanism by which boswellic acid effectively treats asthma is based on reductions of Th2 cytokines via inhibition of pSTAT6 and GATA-3 expression.[139]

Clinical Studies

Anti cancer activity of gum resin

Clinically, BSE decreases the peritumoral edema in glioblastoma patients and reverses several brain metastases in breast cancer patients.[140] Kirste *et al.* conducted a potential, placebo-controlled, pilot trial to examine the effect of extract of *B. serrata* on forty-four patients with primary or secondary malignant cerebral tumors. [41] Patients randomly treated with radiotherapy with either BSE 4200 mg/day or placebo, cerebral edema significantly reduced in 60% of patients treated with BSE and in 26% of patients treated placebo (P =.023).[41]

Biosynthesis of the subclass cysteinyl leukotriene (Cys-LT) in injured brain tissue and specifically that the amount produced by glioma tissue correlates with the malignancy grade of the tumors.[141,142,143] The latter is related to the formation of the so called perifocal edema which is most often causes of neurological symptoms in brain tumor patients.[144,145] They demonstrated that oral ingestion of H15 (BSE) inhibited the generation of Cys-LT in the blood of healthy volunteer suggesting its therapeutic efficacy. Simmet and Winking observed that H15 extract reduced the perifocal brain edema significantly better than high dose of dexamethasone, which is the standard treatment for brain edemas.[146] The antiedemogenic effect of frankincense extract on the central nervous tissue observed by them first time and later on confirmed by others.[147,41]

Xia *et al.* studied the cancer chemopreventive effects of *B. sacra* gum resin hydrodistillates on invasive urothelial cell carcinoma.[84] A 52-year-old Hispanic male presented with hematuria and was later diagnosed with a large invasive high-grade urothelial cell carcinoma (UCC) of the urinary bladder,

but with ambiguous pT1/pT2 staging regarding musclaris propria invasion by UCC. The patient started oral *B. sacra* gum resin (hydrodistillates (BSGRH) administration at 3 mL daily with lifestyle changes, and continued this regimen for 25 months. This index case suggests that BSGRH may have cancer chemopreventive effects on UCC. The use of *Boswellia* derived products in the management of cancer has been well document in other published studies, and boswellic acids have been suggested to be the major component. Demonstration of cancer chemoprevention using BSGRH is one step forward in isolating the key components other than boswellic acids in gum resin of *B. sacra*.

Anti hyperglycemic activity of gum resin

Mehrzadi *et al.* evaluated antihyperglycemic and lipid-lowering effects of *B. serrata* gum resin in type 2 diabetic patients.[148] Fifty-six diabetic patients were randomly allocated to 2 groups to receive 250 mg of the *B. serrata* gum resin or placebo twice daily for 8 weeks in addition to their routine antidiabetic treatments. Although there was a considerable reduction after the intervention in the field of fasting blood sugar, glycosylated hemoglobin, and triglyceride in the *B. serrata* gum resin group, no significant difference was observed in all outcome measures between the 2 groups at the end of the study. The current study showed that 8 weeks of complementary use of *B. serrata* gum resin with a daily dose of 500 mg had no better glucose and lipid-lowering effect than placebo in diabetic patients.

Effect of gum resin on IBD

In a double-blind, placebo controlled study investigating the efficacy of Boswelan in maintaining remission in CD, 82 patients were randomized to either Boswelan (n=42, 3×2 capsules/day; 400 mg each) or placebo (n=40). No differences in the two groups concerning the remission rates were noticed. Regarding safety, no disadvantages of taking the drug compared to placebo were observed. This trial confirmed the good tolerability of Boswelan, although there were no significant differences versus placebo in maintenance of remission.[33]

Gupta *et al.* (2001) conducted an experiments on patients studied here suffered from chronic colitis characterized by vague lower abdominal pain, bleeding per rectum with diarrhoea and palpable tender descending and sigmoid colon.[149] The inflammatory process in colitis is associated with increased formation of LT's causing chemotaxis, chemokinesis, synthesis of superoxide radicals and release of lysosomal enzymes by phagocytes. The key enzyme for LT biosynthesis is 5-LOX. Boswellic acids were found to be non-redox, non-competitive specific inhibitors of the enzyme 5-LOX. They studied the gum resin of *B. serrata* for the treatment of this disease. Thirty patients, 17 males and 13 females in the age range of 18 to 48 years with chronic colitis were included in this study. Twenty patients were given a preparation of the gum resin of *B. serrata* (900 mg daily divided in three doses for 6 weeks) and ten patients were given sulfasalazine (3 gm daily divided in three doses for 6 weeks) and served as controls. Out of 20 patients treated with *B. serrata* gum resin 18 patients showed an improvement in one or more of the parameters: including stool properties, histopathology as well as scanning electron microscopy, besides hemoglobin, serum iron, calcium, phosphorus, proteins, total leukocytes and eosinophils. In the control group 6 out of 10 patients showed similar results with the same parameters. Out of 20 patients treated with *B. serrata* gum resin 14 went into remission while in case of sulfasalazine remission rate was 4 out of 10. As a result gum resin preparation from *B. serrata* could be an effective in the treatment of chronic colitis with minimal side effects. The anal sphincter pressure in the groups treated with *B. serrata* showed a significant increase compared to the colitis group ($P < 0.001$).[149]

Effect of gum resin on asthma

In a double-blind, placebo-controlled study forty patients, 23 males and 17 females in the age range of 18-75 years having mean duration of illness, bronchial asthma, of 9.58 ± 6.07 years were treated with a preparation of gum resin of 300 mg thrice daily for a period of 6 weeks. 70% of patients showed improvement of disease as evident by disappearance of physical symptoms and signs such as dyspnoea, rhonchi, number of attacks, increase in FEV subset1, FVC and PEFR as well as decrease in eosinophilic count and ESR. In the control group of 40 patients 16 males and 24 females in the age range of 14-58 years with mean of 32.95 ± 12.68 were treated with lactose 300 mg thrice daily for 6 weeks. Only 27% of patients in the control group showed improvement. The data show a definite role of gum resin of *B. serrata* in the treatment of bronchial asthma.[38]

Effect of gum resin on osteoarthritis

Kimmatkara *et al.* carried out studies involving a group of 30 patients with osteoarthritis of the knee.[150] All patients received *Boswellia* treatment re-ported a reduction in knee pain, improved knee flexion and walking distance and the incidence of knee joint inflammation was reduced. They concluded that BSE can be recommended in osteoarthritis condition of the knee with possible relaxing use in other arthritis cases. Kizhakkedath (2013) studied the effect of a combination of the common spice *Curcuma longa* and the active principles of *B. serrata* (CB formulation) on 30 osteoarthritis patients divided into two groups of 15 subjects.[151] As a result the CB formulation 500 mg, administered twice daily demonstrated a greater improvement in the treatment of osteoarthritis than celecoxib 100 mg.

Effect of gum resin n multiple sclerosis (MS)

A recent double blind, randomized, placebo controlled human study, suggested that *B. serrata* improved California verbal

learning test and brief visuospatial memory test in relapsing remitting MS patients without major depression who had subjective complaints of cognitive impairment (CI).[152] Sedighi *et al.* demonstrated that *B. papyrifera* showed significant improvement in visuospatial memory but had no effect on verbal memory and information process speed.[153] Farshchi *et al.* reported that *B. papyrifera* affect spatial memory retention irrespective of treatment period.[154]

Conclusion

In conclusion, frankincense tree is widespread in dhofar region. Extract obtained from *boswellia* and its derived compounds have been proven to have extensive medicinal value and therapeutic potential to treat life threatening ailments. The major essential oil component alpha pinene noted to be excellent antimicrobial and anti cancer agent. Different boswellic acids from gum resin of *boswellia* in particular AKBA possess immense anti cancer potential in different tumor models. Overall the active principle of frankincense has enormous potential. However, the exact mechanism of action for their therapeutic potential not well explained and understood. Based on the current review, it is warranted that the detailed study on *boswellia* extract and its derived compounds should be done in preclinical and clinical set up to bring out the real potential.

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Conflicts of interest

There are no conflicts of interest.

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