



Contents lists available at ScienceDirect

## Asian Pacific Journal of Tropical Biomedicine

journal homepage: [www.elsevier.com/locate/apjtb](http://www.elsevier.com/locate/apjtb)Review article <http://dx.doi.org/10.1016/j.apjtb.2017.05.001>

## Phytochemistry and potential therapeutic actions of Boswellic acids: A mini-review

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## ARTICLE INFO

## Article history:

Received 23 Aug 2016

Received in revised form 26 Oct 2016

Accepted 15 Jan 2017

Available online 25 May 2017

## Keywords:

*Boswellia serrata*

Boswellic acids

Inflammation

Leukotriene synthesis

5-Lipoxygenase

## ABSTRACT

The pentacyclic triterpenic acids isolated from the oleo gum resin of various *Boswellia* species are collectively called as Boswellic acids (BA). The oleo gum resin obtained from Indian variety i.e. *Boswellia serrata* (Family – Burseraceae) is commonly known as Salai guggal. The resin fraction of Salai guggal is rich in Boswellic acids and its essential oil is composed of a mixture of mono, di and sesquiterpenes while gum fraction chiefly contains pentose and hexose sugars. This oleo-gum resin is quite popular among traditional practitioners of traditional Chinese and Indian Systems of medicine owing to their wide range of useful biological properties such as anti-inflammatory, anti-arthritic, anti-rheumatic, anti-diarrheal, anti-hyperlipidemic, anti-asthmatic, anti-cancer, anti-microbial anti-fungal, anti-complementary and analgesic activity, etc. It has been used as a herbal medicine since the prehistoric time to cure acute and chronic ailments including inflammatory diseases. Phytochemical investigation of this herbal medicine lead to identification of Boswellic acids which are found to be novel, potent, specific anti-inflammatory agents due to non-redox inhibition of 5-lipoxygenase (5-LO) enzyme. However, the other important targets of Boswellic acids also include topoisomerases, angiogenesis, and cytochrome p450 enzymes. This review is a sincere attempt to discuss and present the current status of therapeutic potential, phytochemical as well as pharmacological profile of Boswellic acids primarily obtained from *B. serrata*.

## 1. Introduction

The herbal extracts prepared from various species of *Boswellia* (family Burseraceae) tree have been used for couple of centuries in traditional medicine worldwide for the treatment of several diseases [1]. *Boswellia* genus comprises of nearly 25 distinct species and some of the important species of this genus include *Boswellia serrata*, *Boswellia sacra*, *Boswellia carterii*, *Boswellia papyrifera*, *Boswellia neglecta*, *Boswellia rivae*, *Boswellia frereana*, and *Boswellia ovalifoliolata*, etc [2–5]. The tree is commonly grown in gulf countries viz. Oman, Yemen

and Southern Saudi Arabia, in East Africa (Somalia and Ethiopia), South Asia and abundantly grows in dry hilly tracts of India [6–9]. The Indian states where it is grown widely include Rajasthan, Gujarat, Maharashtra, Madhya Pradesh, Bihar, Orissa and some parts of Western Himalayas [10]. The dried exudate from the bark of *B. serrata* tree is an oleo-gum-resin which is commonly known as Indian Frankincense, Indian olibanum, Incense or Salai guggal. The dried gum appears in form of lumps or tears which are white-yellow in color. The word frankincense meaning “pure incense” is derived from the ancient French name [11]. In Arabic language, frankincense is also known as “al-luban,” which means “white” or “cream and is a basis for its other name, olibanum [10,12–15]. It is known by the name of Ru Xiang in Chinese [16]. In Ayurveda, an Indian traditional system of medicine, the gum is used to treat a number of inflammatory diseases affecting skin, eye, gums, gastrointestinal tract (GIT) in addition to the respiratory inflammatory disorders such as asthma, bronchitis, laryngitis etc [15].

Salai guggal or oleo gum resin is a mixture of essential oil, gum and resin. The essential oil is chiefly a mixture of monoterpenes, diterpenes and sesquiterpenes. Its essential oil also contains

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Peer review under responsibility of Hainan Medical University. The journal implements double-blind peer review practiced by specially invited international editorial board members.

phenolic compounds and a diterpene alcohol (serratol). Gum portion contains pentose and hexose sugars with some oxidizing and digestive enzymes. Though, the biologically active phyto-constituent boswellic acid is found in resin of almost all species of *Boswellia* which is chemically a pentacyclic triterpene acid [10,16].

A number of review and research articles focusing on pharmacological studies have highlighted the usefulness of boswellic acids in the management of several chronic inflammatory diseases including chronic ulcerative colitis, rheumatoid arthritis, crohn's disease, and bronchial asthma; in addition to its anti-depressive and anti-anxiety effects and beneficial effects in brain tumor patients [17]. The two most potent anti-inflammatory boswellic acids of *Boswellia* are acetyl-11-keto-beta-boswellic acid (AKBA) and 11-keto-beta-boswellic acid (KBA) [18]. In this review, we have summarized the chemistry, pharmacokinetic, clinical outcomes and therapeutic uses of boswellic acids (BA).

## 2. Pharmacognostical characteristics of Indian *Boswellia*

*B. serrata* belonging to the family Burseraceae is a deciduous tree which usually grows up to a moderate height (4–5 m). Like any other medium to large size branching tree, it has a circumference of 2.4 m (av 1.5 m). The thin bark changes its color from greenish gray, yellow or reddish to ash color which can be easily peeled off. The papery barks upon peeling or incision exudates translucent lumps, tears or droplets of white to yellow color gummy oleoresin [19]. The gum is aromatic with balsamic odor and bitter in taste.

Leaves: Odd pinnate, Length: 30–45 cm long, ex-stipulate, variable in shape, Crowded at the end of the branches.

Leaflets: 8–15 in number, 2.5–6.3 × 1.2–3.0 cm, ovate or ovate-lanceolate, rounded base, nearly sessile with short toothed, mostly pubescent.

Flowers: Bisexual, small, white in axillary racemes or panicles at the tip of the branches.

Calyx: 5–6 lobed and small copular.

Petals: 0.5–0.8 cm oblong-ovate with basal disk, white pink color.

Fruits: Cotyledous, trifid, 1.25 cm long, trigonous, obovoid type.

Seeds: Heart-shaped and attached to the inner angle of the fruit, compressed, pendulous.

## 3. Phytochemistry

The different species of *Boswellia* have about 200 phytochemicals in oleo-gum-resin mixture. These compounds include essential oil, pure resin and mucus. The content and composition of oleo gum resin may vary from species to species depending upon age, quality of resin, geographical conditions. The resins of *Boswellia* species chiefly contain higher terpenoids i.e. pentacyclic triterpenes and tetracyclic triterpenes but the former are mainly considered to be responsible for its pharmacological effects [20,21]. Chemically BA is 3-hydroxyurs-12-ene-23-oic acid. The BAs are common chemical characteristic feature of all species of genus *Boswellia*. The six major BAs are;  $\alpha$  and  $\beta$ -Boswellic Acids (BA, 10–21%), Acetylated  $\alpha$  and  $\beta$ -Boswellic Acids (ABA, 0.05–6%), 11-keto- $\beta$ -Boswellic acid (KBA, 2.5–7.5%) and 3-O-acetyl-11-keto- $\beta$ -Boswellic acid (AKBA, 0.1–3%) are present in all *Boswellia* species but in varying quantities

(Table 1) [10]. The content of Boswellic acids in commercially available standardized extracts vary from 37.5 to 65% [22]. AKBA ( $\lambda_{\max}$  250 nm) is white crystalline powder, soluble in chloroform, methanol and almost insoluble in water.

Among all the BAs of *Boswellia*, the two most active, potent and promising anti-inflammatory agents are AKBA and KBA. Some other BAs isolated from *Boswellia* are 9,11-dehydro- $\alpha$ -Boswellic acid and its isomer (9,11-dehydro- $\beta$ -Boswellic acid) and their respective acetylated forms (Acetyl-9,11-dehydro- $\alpha$ -Boswellic and Acetyl-9,11-dehydro- $\beta$ -Boswellic acids). The other chemical contents found in *Boswellia* are Lupeolic acid and Acetyl-Lupeolic Acid, Incensole acetate, Incensole oxide and Isoincensole oxide. Some authors have also reported the occurrence of a pentacyclic triterpenediol mixture of 3 $\alpha$ ,24-dihydroxyurs-12-ene and 3 $\alpha$ ,24-dihydroxyolean-12-ene, Serratol,  $\alpha$ -Thujene, Tirucall-8,24-dien-21-oic acids, oilbanumols D-G,  $\alpha$ -pinene and octyl acetate in the crude extract [23–29]. The presence or absence of 11-keto group in BA affects its potency [30]. Conversion of 11 keto group to 11 methylene group leads to reduction in 5-LO activity, however reduced form became more efficient toward induction of apoptosis and inhibition of topoisomerases [31]. Removal of Acetyl group or reduction of 11 keto group to alcohol in AKBA produces slight decrease in activity of 5-LO inhibition suggesting that backbone of pentacyclic triterpene along with 11 keto group is required for binding to the receptor site to exert anti-inflammatory activity [32].

The essential oil of Salai guggal mainly contains monoterpenoids (pinene, cis-verbenol, trans-pinocarveol, borneol, myrcene, phallendrene, cadinene, verbenone, limonene, thuja-2,4(10)-diene and p-cymene) and small amount of diterpenes.  $\alpha$ -pinene (73.3%) is the major chemical constituent of monoterpenoids [33].

## 4. Pharmacokinetics properties of Boswellic acids

As the KBA and AKBA are highly lipophilic drugs, they have relatively poor absorption through GIT but high retention [34,35]. The elimination half-life of 11-Keto  $\beta$ -Boswellic acid (KBA), is reported to be approximately 6 h. This implies that boswellic acids should be taken every 6 h p.o. to achieve maximum plasma levels [36]. Further, it has been reported that BAs should be taken along with fatty meal as it significantly increases their plasma concentration [37].

Some studies have proved that administration of *Boswellia* extract in a lecithin delivery form markedly enhance the serum levels and subsequent tissue deposition of BAs [38]. The study noted that the use of phospholipid-based delivery system enhanced the absorption while reduces variability [39]. Sharma

**Table 1**

Properties of different boswellic acids (BAs).

Name	M.Wt	Melting Point (°C)	Specific Rotation $[\alpha]_D$
$\alpha$ and $\beta$ -Boswellic Acids (BA)	456.71	226–274	+138°
Acetylated $\alpha$ and $\beta$ -Boswellic Acids (ABA)	498.75	252–255	+138°
11-keto- $\beta$ -Boswellic acid (KBA)	470.70	195–197	+78.5°
3-O-acetyl-11-keto- $\beta$ -Boswellic acid (AKBA)	512.73	771–274	+88.5°

*et al.* used a complexation technique to improve the pharmacokinetic profile especially their poor absorption through the intestine for better bioavailability. The absorption was enhanced by preparing a complex of BA with phosphatidylcholine and ex-vivo drug absorption of prepared complex and plain BA was studied by using an everted intestine sac technique. The obtained results revealed significantly enhanced absorption property of the complex with respect to BA which was attributed to its amphiphilic nature. Due to improved pharmacokinetic and enhanced bioavailability, the complex also showed better anti-inflammatory and hypolipidemic activity establishing the superiority of the complex over plain BA [38].

Several studies clearly demonstrate the detection of six primary BAs namely  $\alpha$ -Boswellic acid,  $\beta$ -Boswellic acid, acetyl- $\alpha$ -Boswellic acid, acetyl  $\beta$ -Boswellic acid, 11-keto- $\beta$ -Boswellic acid, 3-O-acetyl-11 keto- $\beta$ -Boswellic acid in tissues of rats following the oral administration of 240 mg/kg Boswellia (86.97 mg/kg total BAs) [39,40].

BAs undergo extensive metabolism that account for their poor bioavailability in vivo. Phase I metabolism in the liver appears to be the major metabolic pathway for KBA,  $\alpha$  and  $\beta$ -BA. Mono or polyhydroxylated derivatives are the predominant metabolites of these BAs. Metabolism is seemed to take place in non-acetylated BA while acetylated forms (AKBA, Acetyl- $\beta$ -Boswellic acid, and Acetyl- $\alpha$ -Boswellic Acid) are resistant [41,42]. Thus, it was concluded that metabolic pathway of AKBA is different from KBA as it deacetylates to a minor extent to yield KBA. Later on high lipophilicity and poor absorption of AKBA was attributed to its low bioavailability [10].

## 5. Mechanisms of action

BAs act on a variety of targets (Figure 1) specifically on 5-lipoxygenase (5-LO), topoisomerases, angiogenesis, and cytochrome p450 enzymes. In addition, depending on the type of cell affected, BAs may stimulate or inhibit mitogen-activated protein kinase (MAPK), especially p38 [43–46].

### 5.1. 5-LO inhibition

In neutrophils, the 5-lipoxygenases enzyme is the predominant one to convert endogenous arachidonic acid to 5-hydroxyeicosatetraenoic acid (5-HETE) and leukotrienes. They cause vasoconstriction, bronchospasm increased permeability and chemotaxis. BA in dose dependent manner in rat peritoneal neutrophils inhibits the key enzyme for leukotriene synthesis i.e. lipoxygenase. BA is a novel specific non redox inhibitor of 5-lipoxygenase as neither it impair the cyclo-oxygenase and 12-

lipoxygenase enzyme properties nor inhibit the peroxidation of arachidonic acid [37,47].

### 5.2. Leukocyte elastase inhibition

The human leukocyte elastase decreases the elasticity of lungs, constricts the lung passages, damages the secretion of mucous in lungs and decreases the removal of the mucus. BAs reduce the activity of elastase enzyme which is responsible for emphysema [48].

### 5.3. Topoisomerase inhibition

BAs have a dual catalytic inhibitory action on human topoisomerase (I and II $\alpha$ ). BAs not only inhibits DNA synthesis in human leukemia promyelocytic cells in a dose dependent manner but also inhibit the topoisomerase (I and II $\alpha$ ) through competition with DNA for binding the enzyme [44,45,48].

### 5.4. Inhibition of C2 convertase

BA inhibits the C2 convertase enzyme, which has the most significant role in the classical complement pathway for specific immunity. As only the antibody of specific classes formed irresponsive to antigen stimulant and is able to stimulate the pathway, so the classical complement pathway serves the specific immunity [49].

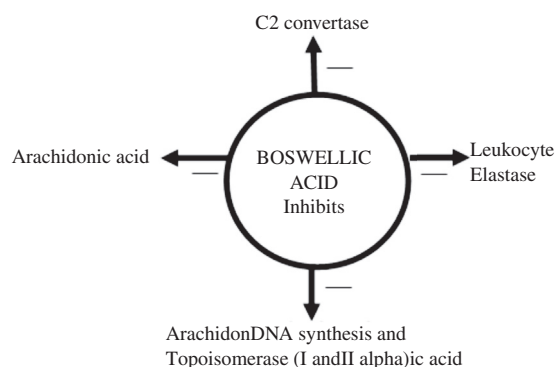
## 6. Pharmacotherapeutic actions of Boswellic acids (BAs)

### 6.1. Anticancer or antitumor activity

Boswellia is a source of one of the most potent anticancerous agent occurring naturally. Methanolic extract of the gum resin exudates of *B. serrata* Boswellin (BE) showed presence of triterpenoids,  $\beta$ -Boswellic acid and its analogs. Huang *et al.* indicated that  $\beta$ -BA and its derivatives (the major constituents of Boswellin) have anticarcinogenic, anti-tumor and anti-hyperlipidemic activities [50]. A number of researchers have also reported that pentacyclic triterpenes of Boswellia are one of the most promising anticancer agents [43,51–53]. The BAs (AKBA, KBA) exerts their cytotoxic effects by inhibiting topoisomerase I & II $\alpha$  leading to 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 [54,55]. Interestingly, a mass spectrometry-based chemoproteomic approach have revealed that  $\beta$ -BAs inhibits protein synthesis by interacting with the ribosomal proteins and thus modulates cancer progression [56].

When HL-60 cells were treated with Acetyl-11-keto- $\beta$ -Boswellic acid (AKBA), prominent morphological changes were observed indicating that the cells underwent apoptosis.  $\beta$ -boswellic acid, 3-O-acetyl- $\beta$ -Boswellic acid, 11-keto- $\beta$ -Boswellic acid, and 3-O-acetyl-11-keto-boswellic acid when examined for their in vitro antitumor activity they were found to inhibit the synthesis of DNA, RNA and protein in human leukemia HL-60 cells in a dose dependant manner. Its effect on DNA synthesis was found to be irreversible [57,58].

Pang *et al.* in 2009 evaluated the role of AKBA obtained from Indian frankincense on the growth of prostate tumor in



**Figure 1.** Mechanism of action of Boswellic acids (BAs).

humans. They found that AKBA significantly inhibited the growth of prostate tumor via inhibition of angiogenesis induced by activation of VEGFR2 and mTOR signaling pathways [59]. An insight into the mechanism of chemopreventive actions of BAs especially AKBA in colorectal cancer cells (CRC) was provided by Takashi *et al.* They found significantly up-regulation of the expression of the two putative tumor-suppressive miRNAs such as let-7 and miR-200 families (CDK6, vimentin and E-cadherin) in various CRC cell lines treated with AKBA. The results of their study confirmed that antitumor effects of AKBA are partly due to up regulation of certain miRNA pathways which make BA an ideal candidate for further studies in the treatment of CRC [60].

Recently, oral administration of *B. sacra* gum resin hydro-distillates (BSGRH) has been shown to possess chemopreventive effects on urothelial cell carcinoma [61]. Similarly, the results of another study showed that supplementation with BAs can augment the antitumor effects of doxorubicin in solid tumors of Ehrlich's ascites carcinoma and can also protect mice against doxorubicin induced cardiotoxicity [62]. Schneider and Weller studied the effect of AKBA and  $\beta$ -BA on nine long term human Glioma stem like cells, five glioma-initiating cell lines and examined the mechanism of acute growth inhibitory, anti-clonogenic properties and assessed the potential synergy with temozolomide (TMZ) or irradiation. The results supported the earlier findings that BA are cytotoxic at low molecular concentration in glioblastoma and their use with irradiation and TMS lead to potential synergistic action. AKBA was found to have the highest activity in six out of nine LTCs and four out of five GICs in testing of acute growth inhibitory and anti-clonogenic properties [63].

## 6.2. Anti-inflammatory and anti-arthritis activity

*Boswellia* species have been used a folkloric medicine since ancient time to treat the inflammatory diseases. The data of numerous scientific studies clearly support the claim that *B. serrata* possess potent anti-inflammatory and anti-atherosclerotic activity [15,64–66].

Plenty of good review articles published in the past have highlighted the potential biological actions and molecular targets of *Boswellia* plants especially anti-inflammatory and chemopreventive activities at cellular level [15,43]. The useful therapeutic actions of BAs in experimental animal studies and clinical trials have also been documented in a systematic way [10]. Inhibition of prostaglandin synthesis seems to play only a minor role as far as the anti-inflammatory effect of BAs is concerned. Contrary to this, inhibition of 5-LO by BAs that lead to a decreased production of leukotrienes has received high attention by the scientific community since a variety of chronic inflammatory diseases are associated with increased leukotriene activity [67].

In one of the clinical trails, *B. serrata* have also shown fair to excellent anti-inflammatory results in 88% of the patients, with no adverse side effects [68]. The anti-inflammatory actions of BAs are observed due to the inhibition of leukotriene synthesis via 5-LO, however, it has no effect on the activities of 12-lipoxygenase (12-LO) and the cyclooxygenase (COX) enzymes. In addition to this, peroxidation of arachidonic acid by iron and ascorbate was also not impaired by BAs. Authors have proposed that BAs inhibit leukotriene synthesis either by blocking the translocation or interacting directly with 5-LO and

thus act as a potent anti-inflammatory agent. Oral administration of BAs changes the electrophoretic pattern of synovial fluid protein and reduces the number of leucocytes. *B. serrata* extract is also used in the treatment of chronic polyarthritis [69,70].

*B. serrata* resin extract inhibit formation of 5-LO products in polymorphonuclear neutrophil leukocytes (PMNL) in a dose dependent manner [44,71].

It has been also reported that pure compound from *B. serrata* extract i.e. BAs produce the anti-inflammatory actions in human peripheral blood mononuclear cells (PBMCs) and mouse macrophages via inhibition of tumor necrosis factor-alpha (TNF-alpha), interleukin-1beta (IL-1beta), NO and mitogen activated protein (MAP) kinases [72]. Khosravi *et al.* in 2011 conducted a double blind randomized clinical trial to assess the efficacy of *Boswellia* in moderate plaque induced gingivitis. They reported that *Boswellia* extract and powder has the ability to lessen the inflammation of periodontium associated with plaque-induced gingivitis due to their anti-inflammatory effects produced through multiple mechanisms [73]. Inhibition of prostaglandin (PG) synthesis is one of the main mechanisms by which pharmaceutical agents produce their anti-inflammatory effect. BA have been reported to inhibit microsomal prostaglandin E2 synthase (mPGES)-1 ( $IC_{50} = 3-30 \mu M$ ), which is the terminal enzyme in the biosynthesis of prostaglandin (PGE2) from cyclooxygenase (COX)-derived PGH2 [74]. mPGES-1, an inducible enzyme belongs to three isoforms of PGE2 synthases and is responsible for the conversion of PGH2 to pro-inflammatory PGE2. Recent studies have revealed that BAs can also inhibit microsomal prostaglandin E2 synthase (mPGES)-1 in cell-free, cellular, and in vivo studies that form the molecular basis for the anti-inflammatory actions of oil-banum [75].

The anti-inflammatory action of BAs in various biological models was thought to be due to the interference with the human glucocorticoid receptor (GR) leading to suppression of the release of pro-inflammatory cytokines and was considered similar to the glucocorticoids (GCs). To establish the molecular targets and binding of natural BAs ligands to GR protein site, Scior *et al.* carried out molecular docking simulation studies by using radiometric binding assays and GR response element-dependent luciferase reporter assay method by employing dexamethasone (DEX) as a functional positive control. It was found that BAs bind strongly to GR though they don't activate GR in comparison to DEX [76].

Notarnicola *et al.* evaluated the efficacy of combination of BA-Mehtylsulfonylmethane (MSM) in comparison to Glucosamine (GS) as an effective supplement in the management of knee arthritis through a prospective randomized clinical trial. The obtained results were found consistent with the anti-inflammatory and chondroprotective effects as established through previous studies. The BA-MSM combination showed promising results and were found to be satisfactory with respect to GS [77].

## 6.3. Hypolipidemic activity

Several scientific studies and research conducted in the past couple of decades have clearly indicated that *Boswellia* is an effective hypolipidemic agent. Water soluble fraction of *B. serrata* extract is known to reduce the level of total cholesterol in experimental animals, thus proving its hypolipidemic potential. Zutshi *et al.* in a study also observed the

antihyperlipidemic activity of Boswellia. Salai gum maintains the serum cholesterol and triglycerides levels of animals in optimum range, which are fed on high cholesterol and saturated fat containing diet [78]. AKBA has been shown to inhibit the activity of NF- $\kappa$ B in atherosclerosis [79].

AKBA is also known to have antiadiposity property by virtue of which it induces lipolysis in mature human adipocytes as shown by an in vitro study carried out by Liu *et al.* Further, it was noticed that this phenomenon was accompanied by down-regulation of PPAR- $\gamma$ 2 expression and loss of phenotypic markers [80].

#### 6.4. Immunomodulatory activity

Cell mediated and humoral components of the immune system and the immunotoxicological properties of BA, was a subject of investigation by many studies [81]. Syrovets and Makare also reported the immunomodulatory activity of BAs [82]. A detailed study on the structural requirements for BAs indicated that of all the six acids, AKBA shows most pronounced inhibitory activity against 5-LO [83]. Studies also showed anti-anaphylactic and mast cell stabilizing or inhibiting mast cell degranulation activity in passive paws anaphylaxis and induced mast cell degranulation of BA [84].

Henkel *et al.* identified that functional target of BAs is the antimicrobial peptide LL-37. It is the only member of the human cathelicidin family that have immune system-modulating properties and believed to play an important role in autoimmune disease development. MALDI-TOF mass spectrometry technique was used to study the binding of BAs to the target source, LL-37 in human neutrophils. This binding lead to inhibition of the functionality of LL-37 and thus could be used for developing agents to LL-37 related disorders [85].

AKBA, KBA and *B. serrata* gum resin extracts exhibit variable actions in the immune system. A mixture of BAs at higher doses can reduce primary antibody titers in the humoral defence system while lower doses show enhanced secondary antibody titers after treatment with sheep erythrocytes. BAs appear to increase lymphocyte proliferation in the cellular defence but in higher concentration effects are inhibitory. The production or release of cytokines is affected by the BAs in addition to their increase activity of phagocytosis of macrophages. Suppressions of the classic way of the complement system was found to be due to inhibition of the conversion of C3 into C3a and C3b [67].

#### 6.5. Hepatoprotective activity

Alcoholic extract of Salai guggal is also reported to have hepatoprotective actions. According to Safayhi hepatoprotection was most probably through the inhibition of 5-LO activity [86]. Zaitone *et al.* assessed the protective effects of BAs in a model of diet-induced Non-alcoholic fatty liver disease (NAFLD) in rodents. NAFLD is closely linked to insulin resistance, oxidative stress, and cytokine imbalance. Hepatic steatosis and inflammation (NFLD) was induced in rats by feeding a high-fat diet (HFD) for three months which was confirmed by deviation of the key liver biomarkers on measurement. Rats treated with BAs (125 or 250 mg/kg) or pioglitazone showed improved insulin sensitivity and a reduction in liver index, activities of liver enzymes, serum TNF- $\alpha$  and IL-6 as well as hepatic iNOS expression compared to control

group. Furthermore, at the cellular level, BAs (250 mg/kg) ameliorated the expression of thermogenesis-related mitochondrial uncoupling protein-1 and carnitine palmitoyl transferase-1 in white adipose tissues. This study provided ample evidence that BAs hold a promise in the clinical management of NAFLD [87].

Data of previous studies have shown that oral administration of *B. serrata* extracts prophylactically can delay the development and progression of hepatic fibrosis in mice [88]. Based on this finding, Khan *et al.* investigated the hepatoprotective efficacy of *B. serrata* extract at two different dose levels of 250–500 mg/kg/day alone and with doxorubicin (DOX) therapy in hepatocellular carcinoma cell lines. They found that oral administration of *B. serrata* extract improved the hepatic functions as indicated by lower values of liver biomarker enzymes in comparison to the DOX treated group. It was proposed that mechanism of this protection was mediated via activation of caspase cascade and induction of apoptosis [89].

#### 6.6. Hypoglycemic effects

Boswellia tree and its gummy resin have been well recognized for its beneficial effects in a large number of diseases, including diabetes mellitus [90]. Azemi and coworkers demonstrated that Boswellia extract possess anti-diabetic effects and has the potential to prevent microcomplications of diabetes in the kidneys and liver [91]. Herbal formulation containing *B. serrata* oleo-gum-resin has been reported to produce significant anti-diabetic activity by affecting hepatic gluconeogenesis, pyruvate carboxylase and phosphoenol pyruvate carboxykinase [92].

A study was designed by Shehata *et al.* to study the involvement of AKBA to prevent induction of autoimmune reactions, insulinitis, and hyperglycemia in the model of multiple low-dose streptozotocin (MLD-STZ) diabetes. Hyperglycemia was induced by injecting i.p. 40 mg/kg STZ daily in male mice for 5 days while the other treatment group received AKBA or KBA along with STZ for 10 days. In STZ treated rats, a significant burst of pro-and anti-inflammatory cytokines in the blood, infiltration of lymphocytes (CD3) into pancreatic islets, and appearance of peri-insular apoptotic cells were recorded. Plasma glucose increased significantly ( $124.4 \pm 6.65$  vs.  $240.2 \pm 27.36$  mg/dl,  $p < 0.05$ ). However, simultaneous treatment with KBA and AKBA showed significantly reduction in pro-and anti-inflammatory cytokines. Also, no infiltration of lymphocytes into pancreatic islets and appearance of peri-insular cells were detected [93].

Ahangarpour and his group conducted a clinical study, the results of which showed that supplementation of *B. serrata* in type 2 diabetic patients for a duration of 6 weeks to type 2 diabetic patients, produce remarkably decrease in fasting blood glucose and increase in insulin level [94]. Encouraged by the results, they further extended the study and investigated the antidiabetic, hypolipidemic and hepatoprotective effects of supplementation of *B. serrata* in 60 type 2 diabetic patients from both sexes. Treatment of diabetic patient with *B. serrata* gum resin extract (p.o. 900 mg) for 6 weeks caused significant increase in blood HDL levels as well as a remarkable decrease in cholesterol, LDL, fructosamine SGPT and SGOT levels. Authors suggested that daily supplementation of 900 mg of *B. serrata* presents a safe and effective means to decrease the risk factors associated with type 2 diabetes. Diabetic patients with *B. serrata* may

maintain their Fructosamine levels, hepatic enzyme activities and lipid profiles close to normal levels and live a quality life [95]. The Antioxidant properties of *B. serrata* extract also seem to play a vital role in their biological actions [96].

### 6.7. Anti-asthmatic activity

Boswellia traditionally has been regarded as a panacea and is known for its effect on the respiratory system. It has been used in steam inhalations, baths, and massages to treat cough, catarrh, bronchitis, and asthma. BAs, the higher terpenoids occurring in frankincense are responsible for the inhibition of leukotriene biosynthesis and, thus by virtue of which, they reduce and prevent the inflammation in many chronic inflammatory diseases like asthma. Several studies demonstrated the anti-asthmatic activity of alcohol extract of Salai guggal (AESG) in patients with prolong history of asthma due to stimulation of MAPK and mobilization of intracellular  $Ca^{2+}$  and inhibition of leukotriene biosynthesis [97].

Ali *et al.* tested the effect of BA extract on 5-lipoxygenase (5-LO) inhibition in an experimental model of pulmonary fibrosis using bleomycin (BL). BA reduced the number of infiltrating cells, lessened the destruction of lung architecture and attenuated lung fibrosis. BA attenuates the BL-induced injury response in rats, such as collagen accumulation, airway dysfunction and injury [98].

Liu *et al.* investigated the anti-asthmatic potential and the mechanism of action of BA in a murine model of asthma. They found that animals treated with BA could suppress allergic airway inflammation, Airway hyperresponsiveness (AHR), ovalbumin-specific IgE and Th2 cytokines secretion in murine model of asthma. Authors postulated that mechanism of asthma attenuation by BA involves inhibition of signal transducer and activator of transcription-6 (STAT6) and GATA-3 expression. The ameliorating effect of BA in allergic reaction makes it a beneficial medication for the treatment of asthma [99].

### 6.8. Anti-microbial activity

A study was conducted to investigate the antimicrobial activities of BAs against microbial pathogens of oral cavity. AKBA displayed an inhibitory effect against all the tested pathogens (MIC of 2–4  $\mu\text{g/ml}$ ). It showed concentration dependent bactericidal activity and also prevented the emergence of mutants of *S.mutans*. AKBA also inhibited the formation of biofilms generated by *S.mutans* and *Actinomyces viscosus* and also reduced the preformed biofilms by these bacteria. The finding of this study suggest that AKBA can be used as a drug candidate for the development of antibacterial agent against oral pathogens and it has great potential for use in mouthwash for preventing and treating oral infections [100]. In another study, the antibacterial activity of BAs was tested against a group of pathogenic gram-positive and gram-negative bacteria. AKBA was found to be the most promising antibacterial agents among all BAs but its antibacterial spectrum was limited to gram-positive bacteria only [101].

### 6.9. Analgesic and psychopharmacological activity

Frankincense is used to treat muscular and arthritic pain in several traditional system of medicine [102–104]. 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. 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 [105]. Menon and Kar found that the *B. serrata* possess marked analgesic activity along with sedative effect. They also observed significant reduction in the spontaneous motor activity after treatment with Boswellia [106].

Harrasi *et al.* also carried out studies on crude extract, essential oils and various fractions of *B. sacra* to justify its Omani traditional use as analgesic. Acetic acid induced writhings and formalin induced pain were used to investigate the analgesic activity of *B. sacra* in mice. Polar sub-fractions of Boswellia sp (2 and 4% methanol) exhibited the highest analgesic activity, almost double of positive control, aspirin. Authors proposed that boswellia seem to produce its antinociceptive properties by both peripheral as well as central mechanism [107].

### 6.10. Clastogenic activity

In Indian and Chinese traditional medicine, consumption of Boswellia species is believed to improve learning, memory, performance and cognitive skills. Traditionally it is used in the elderly for enhancement of memory and advised to be taken by pregnant women to increase the memory and intelligence of their offsprings [108]. Aqueous extract of *B. serrata*, *Spirulina alga* and *Withania somnifera* produce clastogenic effect and has potential to be used in stress relief, memory enhancement and memory boost. BA fraction of *B. papyrifera* also enhances spatial memory retention in male rats after systemic administration. These effects were observed to be dose-dependent and could be due to the interaction of BAs with neurotransmitter signaling cascades or protein kinase pathways in the brain [109].

Mahboubi *et al.* found that combined treatment with *Melissa officinalis* and *B. serrata* extracts could prevent memory loss in scopolamine treated rats. They hypothesized that the protective actions of extracts on damaged brain cells could be due to multiple mechanisms of actions including anti-inflammatory effect [110].

### 6.11. Useful actions on skin and psoriasis

Studies have shown that *B. serrata* extract decreases redness and irritation in the skin and restore an even skin tone. In China, Frankincense has been used to treat skin bruises and infected sores. In addition, AKBA is reported to be an effective topical agent to soften facial lines and relax the skin [111].

In a double blind study, efficacy of a novel BA formulation Bosexil® (lecithin, *B. serrata* resin extract) was evaluated in topical treatment of psoriasis and erythematous eczema in human subjects in comparison with *Vaccinium myrillus* seed oil treatment and placebo. The treatment with Bosexil® formulation improved scales (70%), itch (60%) and erythema (50%) without any case of worsening [112].

Wang *et al.* in 2012 prepared a transdermal patch primarily consisting of AKBA for the effective treatment of psoriasis [113]. Kim in 2014 demonstrated that different compositions of  $\alpha$ -BA and  $\beta$ -BA could exhibit potent activities toward melanin

synthesis collagenase. A patent was filed for these compositions of BAs due to their useful actions on skin whitening and in reducing wrinkle [114].

### 6.12. Activity in Crohn's disease

In traditional Iranian system of medicine, the oleogum resin of *B. serrata* and *B. carterii* is valued for reducing the inflammation and is one of the efficacious remedies for the treatment of inflammatory bowel disease (IBD). The gum resin of *B. serrata* has been shown to be effective in the treatment of chronic colitis, with a few side effects [115]. A comparative study of *B. serrata* extract and masalazine molecule which is commonly used in treating Crohn's disease proved that *B. serrata* was superior on efficacy and safety aspects as compared to masalazine [116].

Hartmann *et al.* in 2014 evaluated the anti-inflammatory and antioxidant effects of *B. serrata* extract 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). The extract administered 2 days before and after the induction of colitis showed a significant decrease in inflammation as compared to that of the control groups ( $p < 0.001$ ). Similarly, extract of *B. serrata* was able to reduce the lipid peroxidation, nitric oxide and iNOS levels following pretreatment and treatment of rats with ulcerative colitis. This study proved that the *B. serrata* extract inhibits inflammatory mediators in acute experimental colitis in rodents and that leads to its protective anti-inflammatory and antioxidant effects [117].

### 6.13. Antidiarrhoeal activity

*B. serrata* extract is quite effective in controlling diarrhea, without causing constipation in the patients with inflammatory bowel syndrome. It inhibits contraction of intestinal smooth muscles and thereby controls acetylcholine and barium chloride induced diarrhea [118].

### 6.14. Diuretic activity

Aqueous extract prepared from oleo gum of *B. serrata* Roxb. at a dose of 50 mg/kg produced significant diuretic effects in experimental albino rats. The aqueous extract on intraperitoneal administration showed natriuretic and kaliuretic effects leading to an increase in urinary output. The extract also did not show any acute toxicity at a dose of 3000 mg/kg body weight [119].

### 6.15. Neuroprotective effects

Progression of several neurodegenerative disorders including Alzheimer's disease (AD) to cognitive, behavioral and functional impairment is mainly due to neuro-inflammation. Boswellia species and their active constituents BAs have been thoroughly investigated for their possible role in neuroprotection owing to their potent anti-inflammatory actions. Frankincense (oilbanum) is reported to protect against the streptozotocin induced AD in a rat model by virtue of their antioxidant, anti-inflammatory and anti-acetylcholinesterase activities [120,121]. Ding *et al.* evaluated the neuroprotective effects of AKBA and KBA against ischemic brain injury. They provided clear cut evidence that neuroprotection by both BAs in oxidative stress induced ischemic injury is via their activating effect on nuclear factor

erythroid-2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) pathway [122,123].

Recently, a research study by Sayed and Sayed investigated the effect of monotherapies with AKBA and a selective cyclooxygenase-2 (COX-2) inhibitor (celecoxib) and compared the effects with the combination therapy of AKBA, a 5-lipoxygenase (5-LO) inhibitor and celecoxib as dual enzyme inhibitors. An intraperitoneal injection of lipopolysaccharide (LPS) was used to induce cognitive dysfunction in mice. Molecular changes resulted following LPS and drug treatment were assessed by measuring glutamate, tumor necrosis factor-alpha (TNF- $\alpha$ ) levels and by performing immunohistochemical investigations of amyloid beta peptide (A $\beta$ ). Authors observed that co-administration of AKBA and celecoxib have a potentiating protective effect in cognitive impairment in mice induced by LPS. The combination therapy was able to reverse the behavioral and molecular changes caused by LPS cognitive dysfunction in mice. The study provides evidence that anti-inflammatory and antiglutamatergic pathways are possibly implicated in this neuroprotective effect of AKBA [124].

## 7. Safety and toxicology

BAs are found to be safe in acute, sub-acute and chronic models. Sign of toxicity and severe side effects with *B. serrata* are rare ( $LD_{50} > 2$  g/kg). These side effects include very mild gastrointestinal upset (diarrhea), urticaria, nausea and skin rashes. Contact dermatitis may be observed by topical administration of *B. serrata* extract [125–127].

## 8. Conclusion

Frankincense, once used in religious ceremonies and valued as gold in trading, has enjoyed popularity in both traditional system and modern medicine due to its numerous beneficial therapeutic properties. BAs, the pentacyclic triterpenoids, are the bioactive phytoconstituents of boswellia of which AKBA has shown promising results in experimental and clinical studies. It is considered as the potential pharmacophoric molecule of natural origin that can play a vital role in drug discovery of anti-inflammatory and chemotherapeutic agent(s). Though, the standardized extract preparations of Indian and Chinese Boswellia are available in international market for the treatment of inflammatory disorders but pure AKBA preparations are yet to enter the market. Future challenges lies in understanding the molecular mechanisms at cellular level, drug–drug interactions, development of methods to improve the pharmacokinetic properties especially oral bioavailability and formulation of a stable preparation.

## Conflict of interest statement

We declare that we have no conflict of interest.

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