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FROM PRECLINICAL TO CLINICAL EVIDENCE: EXPLORING THE MULTIPLE PERSPECTIVES AND HEALING POWER OF *BOSWELLIA SERRATA* ROXB. EX COLEBR

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SUMMARY

Boswellia serrata Roxb. ex Colebr. is a species belonging to the *Burseraceae* family, typical of dry environments of the Indian region. The oil-gum-resin, obtained from the trunk and thick branches, is known in phytotherapy for the volatile fraction which contains up to 70% terpenes. The most important and characteristic constituents are represented by pentacyclic triterpenes, named boswellic acids. *B. serrata* is known for multiple beneficial effects, mainly correlated to anti-inflammatory activity. This review aims to provide a comprehensive overview on the activities and potential applications of *B. serrata* based on clinical and preclinical evidence.

An up-to-date literature review of preclinical and clinical studies related to the applications of *B. serrata* preparations in different pathological conditions was conducted using the main databases of scientific literature.

A body of evidence point out the role of *B. serrata* extracts and its active constituents in the treatment of several inflammatory diseases. In particular, clinical trials revealed its use as a topical remedy of skin diseases, such as eczema and psoriasis, and internally in the treatment of asthma, intestinal and osteoarticular inflammatory diseases. Preclinical findings highlighted the positive effects of *B. serrata* extracts in cardiovascular and neurodegenerative diseases, and in cancer. Finally, *B. serrata* finds application as a feed additive in veterinary use.

Although some limitations must be overcome, such as poor bioavailability, evidence supports that *B. serrata* is a promising medicinal plant. Furthermore, the use of *B. serrata* appears to have a favorable toxicological profile, but caution may be necessary regarding potential botanical-drug interactions.

Key words
Boswellia serrata; boswellic acids; natural compounds; inflammation; degenerative diseases.

List of abbreviations
5-LOX: 5-lipoxygenase; ABAs: acetyl boswellic acids (acetyl α- and β-boswellic acid); AD: Alzheimer's Disease; AKBA: 3-O-acetyl-11-keto-β-boswellic acid; ALS: amyotrophic lateral sclerosis; Aβ: amyloid beta peptide; BA: boswellic acids (α- and β-boswellic acid); CD: Crohn's Disease; cGMP: cyclic guanosin-3',5'-monophosphate; COX-1, COX-2, Type 1- and 2- cycloxygenase; EMA: European Medicines Agency; eNOS: endothelial nitric oxide synthase; GIIA: Group II secreted phospholipase A2; IC50 value: inhibitory concentration (50%); iNOS: inducible nitric oxide synthase; KBA: 11-keto-β-boswellic acid; LD50: lethal dose (50%); MS: multiple sclerosis; OA: osteoarthritis; PFC: Prefrontal cortex; ROS: reactive oxygen species; UC: Ulcerative Colitis; VAS: Visual Analog Scale; WOMAC: Western Ontario and Mcmaster Universities Ostheoarthits Index.

INTRODUCING BOSWELLIA: BOTANICAL DESCRIPTION, PHYTOCHEMISTRY AND REGULATORY ASPECTS

Boswellia serrata Roxb. ex Colebr. is a species belonging to the *Burseraceae* family, commonly found growing in dry environments and at the margin of forests in the Indian region, from Punjab to Bengal in the north to peninsular India in the south (1). The resin, more precisely the oil-gum-resin naturally obtained from the trunk and thick branches is known in phytotherapy as Indian frankincense, in pharmacopoeias and official texts as *Gummi Boswellii* (2) or as *Olibanum indicum* (3). Former botanical synonyms of *B. serrata* are *B. glabra* Roxb. and *B. thurifera* (Colebr.) Roxb.
A distinct species of *Boswellia* genus known in folk medicine and taken into consideration as a source of ceremonial incense is generically referred as frankincense (properly African frankincense), and thus confused in this context with *B. serrata*, is *Boswellia sacra* Flueck. (syn. *Boswellia carteri* Birdw.), native in the Arabian Peninsula and the Horn of Africa (4).
B. serrata is a deciduous tree, up to 18 m in height and up to 2.4 m wide in trunk diameter. Leaves are imparipinnate, up to 37 cm long and have ovate or ovate-lanceolate leaflets with serrate margins. Flowers are small, white, grouped in axillary racemes or panicles with 5 hairy petals and sepals and stamen, directed inwards. The fruit, 3-4 in number, is a drupe 9-14 mm long, trigonous, scarlet when unripe and white at maturity. The bark is grey, thick, and aromatic. The resin exudes from natural or artificial incision and solidifies to open air into an irregular mass (5). It is reddish-orange brown to greenish yellow, or light yellow. It occurs in small, ovoid, fragrant tears, sometimes agglomerated; the surface is waxy and translucent. *Gummi boswellii* burns readily and emanates an aromatic, characteristic balsamiferous odor; the taste is agreeable (2).
B. serrata gum-resin contains a volatile fraction, a triterpenic part, and gum; this latter is a complex mixture that is not clearly identifiable, mainly based on carbohydrates (6). According to the Monograph on Selected Medicinal Plants issued by the World Health Organization (WHO), the volatile fraction (up to 9%) consists in α-thujene (50-61% of the fraction), sabinene (5%), α-pinene (8%), phellandrene (2%), and minor monoterpenes. The triterpenic fraction of boswellia gum-resin is characteristic of the species and the phytochemical signature of pentacyclic triterpenes may be considered as the chemical marker of this herbal product. Specifically, boswellia gum-resin contains triterpenes in large quantities, up to 70% of total terpenes. The most important and characteristic constituents are pentacyclic triterpenes, called boswellic acids (BAs), based on 3-hydroxyurs-12-ene-23-oic acid skeleton. The major BAs found in boswellia gum-resin are: α- and β-boswellic acid (up to 25%, mainly β-boswellic acid), acetylated α- and β-boswellic acid (ABAs, up to 8%), 11-keto-β-boswellic acid (KBA, 0.5–7.5%) and 3-O-acetyl-11-keto-β-boswellic acid (AKBA, 0.1–3%) (7-9). KBA and AKBA (minimum 1% of each, dry basis) are the two markers considered

for the quality of *Olibanum indicum* according to the European Pharmacopoeia 11th ed.

B. serrata gum-resin is an herbal material registered as medicine and it is enlisted in the previously mentioned European Pharmacopoeia 11th ed., as well as in several Asian pharmacopeias. In the European Union (EU) it is an orphan drug used in the treatment of peritumoral edema derived from brain tumors as a powdered drug (9) (see section 9.2).

Boswellia gum-resin is also widely used as food supplement in the EU and in many other countries. In Italy, one of the most important markets for food supplements and where health claims are linked to specific botanicals (10), boswellia is claimed to maintain osteoarticular functionality, to counteract states of tension, and to support gastrointestinal health (11). *B. sacra* is also used in the EU as food supplement, with the same health claims referred to *B. serrata* (11).

In the sector of food supplements, boswellia gum-resin is mainly used as a dry extract, standardized in total BAs. Depending on the method of quantification, BAs in boswellia extracts may vary between 3% to up to 43% by using HPLC method (12), even if many products are still analyzed by means of UV methods and they are labelled to contain up to 65-70% of total BAs (13).

While boswellia preparations and isolated compounds have been tested *in vitro* and *in vivo* models, only powdered drugs and extracts containing the whole boswellia phytocomplex have been considered in clinical trials.

MULTI-TARGET EFFECTS OF BOSWELLIC ACIDS

The multiple beneficial effects described for *B. serrata* preparations are primarily associated with anti-inflammatory action; indeed, BAs have been shown to regulate several mechanisms of the inflammatory pathway, including inhibition of leukotrienes, prostaglandin synthesis, inhibition of the complement system, and decreased production of pro-inflammatory mediators (14). AKBA inhibits 5-lipoxygenase (5-LOX) by a selective, enzyme-directed, non-redox, non-competitive mechanism, with IC_{50} from 1.5 μM to 8.0 μM (15). Furthermore, an *in silico* drug-likeness prediction and molecular docking identified high binding affinity of AKBA towards COX-2, iNOS, and TNF-α (16). Elemolic acid, another triterpenoid of *B. serrata*, was shown to irreversibly bind to Group II secreted phospholipase A2 (GIIA) with IC_{50} value of 5.70 ± 0.02 μM (17). The anti-inflammatory action of BAs or other constituents of *B. serrata* extract are also linked to the inhibition of NF-κB. Mechanistically, AKBA inhibited NF-κB activation through the suppression of Akt, resulting in downregulated IκBα ubiquitination and degradation and subsequent reduction in p65 phosphorylation, nuclear translocation and NF-κB mediated gene expression (18). Besides anti-inflammatory activities, *B. serrata* extract could also directly quench intracellular reactive oxygen species (ROS) in macrophages, modulating oxidative stress and ROS-activated signaling pathways. Additionally, BAs protect against oxidative stress-induced damage, *via* upregulation of Nrf2 and HO-1 (19).

Collectively, the anti-inflammatory and antioxidant activities of BAs may also contribute to an anti-diabetic effect with studies demonstrating a glucose-lowering activity together with the regulation of autoimmunity in pancreatic islets. Furthermore, the anti-diabetic effects of BAs and KBA have been associated with inhibition of the enzyme dipeptidyl-peptidase 4 (DPP-4) with IC_{50} values of 3.06 ± 0.85 and 1.65 ± 0.065 μM, respectively (20).

In the brain, other mechanisms underlying the beneficial effects of BAs include a decreased glial cell activation and upregulation of antioxidant proteins, resulting in neuroprotection (21). In a rotenone-induced model of Parkinson's disease, *B. serrata* extract increased AMPK phosphorylation, reducing p-mTOR and α-synuclein (22). In a streptozotocin-induced model of Alzheimer's disease BAs significantly reduced phosphorylated tau and enhanced reelin expression (23).

B. serrata extract exhibits strong antibacterial effects, often ascribed to the presence of phenolic acids (24). Additionally, the ability to inhibit the formation of bacterial biofilm is attributed to the high concentration of terpenes in *B. serrata* extracts (25). A target-based screening of 664 natural compounds identified three BAs as inhibitors against MurA *Escherichia coli*, with an IC_{50} 7–11 μM (26). KBA has been tested *in vitro* against malaria, where it was found to inhibit heme detoxification pathways leading to an increase in ROS, detrimental to *Plasmodium falciparum* (27). Worthy of mention, several studies have recently investigated the effects of BAs on the SARS-CoV-2 virus. Caliebe *et al*. reported that BAs bind to three functional proteins of the virus, responsible for adhesion and replication, with micromolar binding affinity (28). In **figure 1** the major constituents of *B. serrata* and putative mechanisms of action are displayed.

METHODOLOGY

The literature research was conducted by researchers with diverse backgrounds and expertise in the fields of neuroscience, cancer, dermatology, cardiovascular, veterinary, phytochemistry, and molecular biology. Clinical and preclinical studies were searched on scientific literature databases including PubMed, Google Scholar, Embase, Web of Science, Cochrane Library, Medline, by using the following keywords: boswellia, boswellia serrata, boswellic acids, olibanum, frankincense.

The inclusion criteria set by authors for the initial selection of papers were:

- availability of full texts in English language;
- papers published from 1980 until March 2023.

More than 1200 papers were retrieved from databases.

A subsequent manual screening was set in order to filter only clinical trials: 72 papers were found eligible for accurate analysis.

Authors set to account for only topics where at least one clinical trial with adequate methodology and published in a high rank journal was found and if pre-clinical data was found to support the specific indication. The following topics were selected: asthma, intestinal inflammation, osteoarticular inflammation, cardiovascular disease, cancer, cognitive decline, skin disorders.

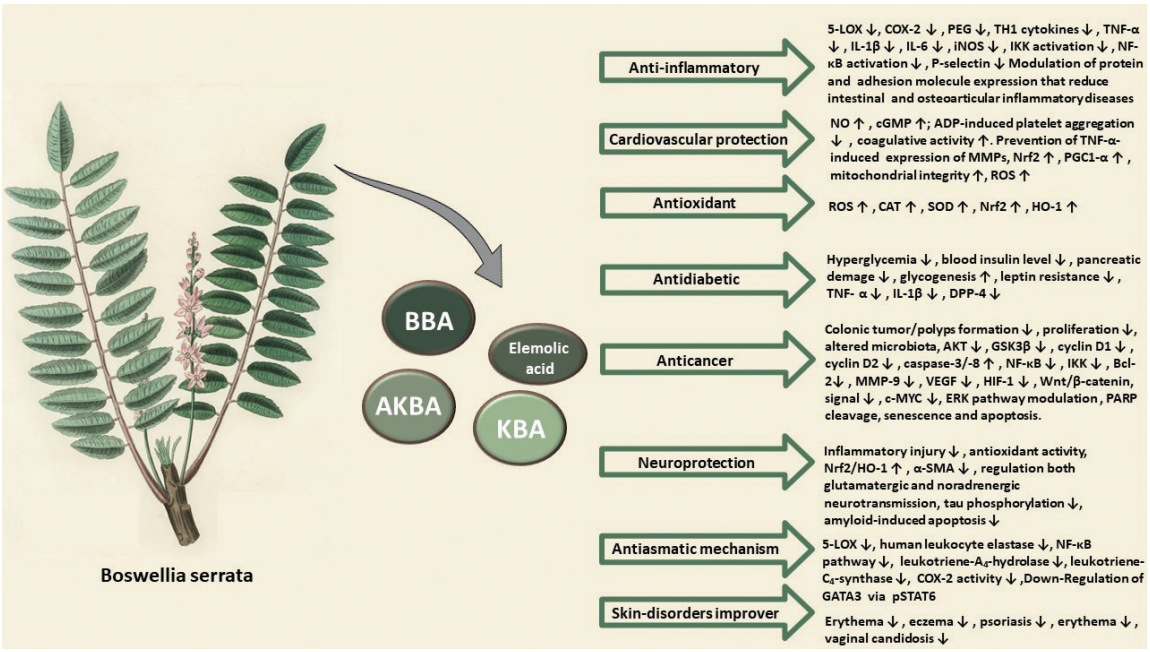

Figure 1. Main secondary metabolites present in *B. serrata* and their beneficial effects.

Authors chose to complete this review by adding a specific section on the veterinary use of boswellia and a discussion on safety.

BOSWELLIA IN ASTHMA

Extracts from the *B. serrata* gum-resin and some of its constituents, like KBA and AKBA, have shown promise as candidates for treating asthma since they act on the immune system in different ways.

Preclinical evidence

Interestingly, accumulating evidence indicates that 5-LOX strongly influences the onset and progression of airway inflammation, as 5-LOX and its products (leukotriene B4 and cysteinyl leukotrienes) are important smooth muscle constrictors of airways and the microvasculature (29). Specifically, *B. serrata* can prevent cytokine production and release by inhibiting 5-LOX, as well as human leukocyte elastase and the NF-κB pathway, leading to downregulation of TNF-α, IL-1, IL-2, IL-4, IL-6, and IFN-γ (30-32). A recent study investigated the structural changes and molecular mechanism of 5-LOX inhibition by AKBA, demonstrating that this molecule inhibited the formation of 5-LOX products through allosteric modulation and induced a switch from pro-inflammatory leukotriene production to anti-inflammatory selective modulators (33). Similarly, the purified fraction of *B. serrata* ethanolic extract reduced leukotriene-A_4-hydrolase, leukotriene-C_4-synthase, and COX-2 activity in HL-60 cell lines. These results were confirmed by an *in vivo* investigation on BALB/c mice, in which the intragastric administration of *B. serrata* significantly reduced lung inflammation (34). Furthermore, it was demonstrated that *B. serrata* effectively reduced asthmatic inflammation by downregulating GATA3 via pSTAT6 (35-36).

Clinical evidence

Treatment with *B. serrata* was demonstrated to be effective in bronchial asthma management (37-39), reducing the need for the standard therapeutic approaches of long-acting β_2-agonist and corticosteroid inhalation (40). Indeed, the use of non-specific β_2-agonists may result in cardiovascular and neurological side effects (41), and the use of corticosteroids in children has been associated with the suppression of growth (42); hence new and safer therapeutic approaches are demanded. Additionally, the combination of *B. serrata* gum-resin with *Aegle marmelos* (L.) Corrêa fruit extract (AlvioLife®) significantly normalized Th1/Th2 cytokine balance and granulocyte infiltration in bronchoalveolar lavage fluid of Sprague Dawley rats. These results were confirmed in a placebo-controlled double-blind clinical trial in which administration of AlvioLife® was found to be effective in managing mild to moderate asthma (43).

BOSWELLIA IN INFLAMMATORY BOWEL DISEASE

Crohn's Disease (CD) and Ulcerative Colitis (UC), both autoimmune inflammatory bowel diseases (IBD), have been researched to be treated with *B. serrata* and BAs (44-45).

Preclinical evidence

The activity of *B. serrata* is attributable to the modulation of the expression of proteins and adhesion molecules involved in the main inflammatory pathways, as demonstrated by numerous *in vitro* studies (45-47). *B. serrata* extract and AKBA were shown to prevent inflammation- or ROS-induced loss of intestinal barrier function in Caco-2 cell monolayers. Both *B. serrata* and AKBA attenuated NF- κB signaling and prevented the loss of tight junction proteins occludin and ZO-1, both of which are dysregulated in IBD (47). Notably, the anti-inflammatory activity of *B. serrata* is not only regarded for its role in altering IBD pathogenesis, but also in improving the quality of life of patients with IBD and irritable bowel syndrome through the management of gastrointestinal pain (48-49).

Clinical evidence

Casperome®, a phytosomal formulation of *B. serrata* enriched in AKBA, was tested in pa-

tients in the minimally symptomatic remission phase of UC. Casperome® supplementation in 22 patients for 4 weeks resulted in a significant improvement in bloody stools, anemia, and abdominal pain, leading to a reduction in the need for medical attention or standard drug therapy for the management of UC (50). Casperome® supplementation also resulted in a significant reduction in fecal calprotectin, a biomarker of neutrophilic inflammation in the gastrointestinal tract. In a randomized double-blind study, a boswellia extract was compared with the standard anti-inflammatory medication mesalazine in terms of efficacy in the treatment of CD. Crohn's Disease Activity Index (CDAI) was assessed for 44 patients treated with *B. serrata* extract and 39 treated with mesalazine. It was determined that the clinical effects of *B. serrata* and mesalazine were similarly beneficial, however with an improved risk-to-benefit ratio for *B. serrata* treatment due to its favorable safety profile (51). In CD, another study compared boswellia to placebo, confirming excellent pharmacological tolerability of the extract and minimal adverse effects (52).

BOSWELLIA IN OSTEOARTICULAR INFLAMMATORY DISEASES

Numerous randomized controlled studies researched the safety and efficacy of *B. serrata* extract in the treatment of osteoarthritis (OA) (53-60).

Clinical evidence

Aflapin®, an extract of *B. serrata* gum-resin standardized to 30% AKBA was administered for 30 days to 35 participants in a randomized controlled trial. Subjects were evaluated in terms of pain and physical functions, using Visual Analog Scale (VAS) and Western Ontario and WOMAC scale (Western Ontario and McMaster Universities Ostheoarthits Index). Subjects receiving 100 mg of daily Aflapin® displayed significant improvement in pain score within five days of treatment. Aflapin® supplementation downregulated expression of circulating inflammatory factors and reduced pain, stiffness, and total WOMAC scores (57).

Another standardized extract of *B. serrata*, 5-Loxin® (enriched in AKBA 30%) was tested at the doses of 100 and 250 mg in a 90-day double-blind, randomized placebo-controlled study, to evaluate its effect in the treatment of knee OA. Both doses reduced pain and improved physical functioning in OA patients (58).

5-Loxin® was compared with Aflapin® in the treatment of OA of the knee in a 90-day randomized placebo-controlled trial. Here, 60 subjects were treated with a dosage of 100 mg for both compounds. This study highlighted the potential efficacy of both formulations in OA patients; in particular, Aflapin® significantly improved joint function and reduced clinical pain scores as early as after 1 week of treatment (59). Notably, however, both formulations displayed significant efficacy over the placebo-treated group.

Boswellin®, another *B. serrata* extract containing AKBA and β-BA, was tested to demonstrate the efficacy of its supplementation. A total of 48 patients with OA of the knee were randomized and allocated to the *B. serrata* extract or placebo group for a period of 120 days. Results revealed that *B. serrata* extract treatment improved the physical function of the patients, reducing pain and stiffness compared with placebo. In particular, the radiographic analysis showed an improved knee joint gap. Moreover, *B. serrata* extract reduced the serum level of highly sensitive C-reactive protein and no adverse events were reported (60).

BOSWELLIA IN CARDIOVASCULAR DISEASES

Despite a wide pharmaceutical armamentarium, cardiovascular diseases are among the most frequent causes of death in the world and great efforts are spent to develop new chemical entities or explore the efficacy of natural compounds and their mechanisms of action (61). In this context, *B. serrata* has shown positive effects on the cardiovascular system.

Preclinical evidence

In an animal model of blood stasis, β-BA ameliorated plasma coagulation parameters, protected endothelium, and prevented blood stasis. Moreover, β-BA significantly increased nitric oxide (NO) and cyclic guanosin-3',5'-monophosphate (cGMP) levels in the carotid artery of blood stasis rats. Conversely, the knockdown of eNOS abolished the protective effects of BA in rats, as well as in HUVEC cells under oxygen and glucose deprivation, suggesting that the NO pathway is a crucial way through which BAs may produce vasodilation and play antiaggregant effects (62). Furthermore, *B. serrata* gum-resin containing high levels of AKBA and other BAs, but also a significant quantity of phenolic compounds, almost completely inhibited ADP-induced platelet aggregation and prolonged coagulative activity (63). Beyond the improvement of NO bioavailability, *B. serrata* is well-known for its anti-inflammatory profile and it might be another mechanism responsible for the protection of endothelial vasculature. Indeed, a *B. serrata* extract prevented the TNFα-induced expression of matrix metalloproteinases (MMPs) in human microvasculature endothelial cells (64). Accordingly, in primary culture of porcine aortic endothelial cells a hydroenzymatic extract of *B. serrata* improved cell viability following lipopolysaccharide (LPS) challenge in a concentration-dependent manner and did not show any toxic effect. On the other hand, it had no effect on cell migratory capacity (64-65). Moreover, AKBA was demonstrated to alleviate damage in H9c2 cells subjected to LPS-induced inflammation and cytotoxicity. A clear reduction of inflammatory markers (IL-6, TNF-α, IL-1β, and COX2) was found, together with a concentration-dependent enhancement of cell viability (66).

Of note, AKBA showed cardiac protection in *in vitro* and *in vivo* ischemic-like models; in particular, in isoproterenol-induced myocardial infarction AKBA alleviated mitochondria-dependent oxidative stress through the enhanced expression of PGC-1α and Nrf2; moreover, in H9c2 cells AKBA improved mitochondrial integrity and inhibited ROS production (67).

Taken together this evidence leads to suppose that *B. serrata* may be considered an interesting remedy for the prevention of cardiovascular diseases and reduction of the atherogenic risk.

Clinical evidence

Findings from clinical trials are sparse. Interestingly, Baram et al. published a report in 2019 that demonstrated that treatment with BAs improved clinical outcomes in the early phases in 80 ischemic stroke patients. Following 7 days of treatment with BAs, the levels of plasma inflammatory markers TNF-α, IL-1β, IL-6, IL-8, and PGE2 were significantly decreased (68).

BOSWELLIA IN CANCER

Evidence suggests that *B. serrata* and its constituents have been found to have significant effects on various tumor types, particularly on tumor growth and metastasis.

Preclinical evidence

BAs demonstrated *in vitro* cytotoxic activity against several cancer cell lines, such as breast, brain, cervical, bladder, lung, melanoma, prostate, or hematopoietic tumors (69-70). KBA and AKBA induced programmed cell death in triple-negative breast cancer cells by upregulating the PERK-mediated ER-stress unfolded protein response (UPR) pathway. (71-72) The *B. serrata* gum-resin demonstrated apoptotic and cytostatic activity against glioma cells, in association with AKBA inhibiting the ERK signal transduction pathway (73-74). *B. serrata* derivatives caused PARP cleavage leading to cell cycle arrest and DNA fragmentation in cervical cancer cell models (75). Furthermore, the anti-proliferative effect of boswellia extended to liver and lung cancer cell lines, whereby BAs induced apoptosis and cell cycle arrest (76-78).

Indeed, several studies have shown the anti-proliferative effects of *Boswellia* spp. ex-

tracts and their phytoconstituents in liver, colon, gastric, and pancreatic cancer cells (79-80). However, AKBA is the most investigated compound. Particularly, in liver cancer, AKBA has been reported to induce both senescence and caspase-dependent apoptosis (79, 81). A pro-apoptotic effect was also observed in colorectal, pancreatic, and gastric cancer cells due to the modulation of several pathways involved in proliferation and metastasis, including Akt/mTOR, NF-κB, and PTEN/Akt/COX-2 (79, 82-83). AKBA also chemosensitized cancer cells toward cisplatin and gemcitabine treatment (79, 82). Compounds other than AKBA have been investigated, but their anti-proliferative properties have been studied at higher concentrations, making them less effective (79, 84-85).

Boswellia extracts and isolated components, especially AKBA, are also able to inhibit tumor growth *in vivo* (79). This activity is principally reported in glioblastoma, but experimental data indicate promising effects for cancers. Indeed, AKBA significantly inhibited the growth of tumors generated in xenograft or homograft models from glioblastoma (86), prostate (87), ovarian (88), or colorectal cancer cells (89), or orthotopically implanted tumors (90), at doses ranging from 20 to 200 mg/kg i.p., alone or in combination with curcumin (89) or radiation (86). *Per os*, AKBA (50 mg/kg) effectively reduced the incidence of polyps in APCMin/+ mice (91) and *B. serrata* extract (0.25 or 0.5%) reduced inflammation-associated colon carcinogenesis induced by azoxymethane/dextran sulfate sodium (92).

Clinical evidence

Clinical trials on the anticancer effects of *B. serrata* are still in their early stages. The ClinicalTrials.gov registry contains four clinical studies investigating the influence of boswellia on breast, brain, and central nervous system tumors (as of March 2023). Three of them test dietary supplements comprising boswellia extracts and one aims to determine whether oral administration of *B. serrata* (800 mg, three times a day) causes changes related to angiogenesis, apoptosis, and cell proliferation in breast cancer patients before surgical resection (registration number NCT03149081).

BOSWELLIA IN COGNITIVE DECLINE

The polypharmacology displayed by *B. serrata* phytoconstituents against cognitive disorders has been extensively demonstrated, mainly with a focus on their anti-inflammatory activity.

Preclinical evidence

It is well known that LPS-induced neuroinflammation increases pro-inflammatory cytokines such as TNF-α, IL-1, IL-2, IL-6, IFN-γ, ICAM-1, and complement system factors. AKBA treatment suppressed LPS-induced neuroinflammation via regulation of NF-κB signaling resulting in improved synaptic plasticity, behavior, and cognition *in vivo* (93-97). In addition, *B. serrata* extract was found to improve cognitive deficit in Alzheimer's Disease (AD). Both chemical-induced and transgenic models of AD were positively improved with BAs treatment (23, 98-100). The proposed mechanisms include the reduction of ROS, pro-inflammatory cytokines, tau phosphorylation, amyloid-β-induced apoptosis, and the antagonism of acetylcholinesterase (98, 100-103). Interestingly, depressive symptoms associated with AD could also be regulated by AKBA. This effect is related, among others, to neurotransmitter regulation affecting both glutamatergic and noradrenergic neurotransmission (104). AKBA prevented the depressive behaviors induced by intracerebroventricular injection of soluble Aβ by reducing heightened glutamate and kynurenine levels in prefrontal cortex and hippocampus as well as downregulating the expression of GFAP and NF-κB (105). Excess glutamate release is also modulated by AKBA or by *B. serrata* extract activity against excitotoxicity induced apoptosis (106, 107).

Notably, the neuroprotective effects of boswellia have also been documented in Parkinson's disease (PD) animal models in which boswellia extracts can alleviate experimental dopaminer-

gic neuronal loss, modulate autophagy, reduce oxidative stress and inflammation and reduce α-synuclein accumulation (108, 109).
Multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) are among the neurodegenerative diseases studied to be positively impacted by *B. serrata* constituents. AKBA produced neuroprotective effects in animal models of MS as demonstrated by an increase in motor and memory scores (110). Indeed, in an ethidium bromide-induced model of experimental MS, AKBA promoted neuroprotection through the induction of the Nrf2/HO-1 antioxidant signaling pathway (110). Similarly, AKBA was described to promote a neuroprotective effect in a methylmercury-induced model of ALS. In ALS, AKBA also activated the Nrf2 pathway thereby promoting antioxidant, anti-inflammatory, and detoxifying effects (111).
Furthermore, several researchers described the promnesic activity of boswellia extracts and BAs in both adult and aged rodents. Various mechanisms have been reported from BDNF regulation to the promotion of axonal outgrowth and branching (96, 112-116).
Cognitive functions are also regulated by neurotransmitter signaling, and many neuropsychiatric and neurodegenerative disorders result from imbalances in neurotransmitters. Adake *et al.*, reported the role of *B. serrata* in various psychiatric disorders, such as depression and anxiety in animal models, by modulating multiple neurotransmitter levels in the brain (117). Accordingly, AKBA showed anxiolytic activity in mouse models (118), and by reducing astrocyte activation and NF-κB activation, AKBA was able to revert an *in vivo* Aβ-associated depressive-like phenotype (119).

Clinical evidence

Data pertaining to the effects of boswellia in improving cognitive function was identified in clinical studies. Meshkata et al. observed, in a pilot clinical trial, the positive effects of *B. serrata* extract in ameliorating cognitive functions in individuals who experienced traumatic brain injury (120). Results were confirmed by a pilot clinical study where *B. serrata* promoted neurological recovery following diffuse axonal injury (121).
Moreover, cognitive assessment in MS patients revealed that the oral administration of a closely related botanical preparation of *B. papyrifera* significantly improved visuo-spatial memory but had no effect on verbal memory and information processing speed (122).
B. serrata extract showed positive effects in age-associated memory impairment: a randomized controlled study highlighted that supplementation of *B. serrata* combined with *Melissa officinalis* supplementation in older adults significantly increased auditory immediate and immediate memory compared to placebo (123).
Worthy of consideration is the application of *B. serrata* in the treatment of cerebral edema in patients undergoing radiation therapy for brain tumors, often associated with cognitive dysfunction (124). In 2002, *B. serrata* resin extract was classified by the European Medicines Agency (EMA) as an "orphan drug" for the treatment of brain edema resulting from brain tumors, based on pharmacopoeia requirements (125, 126). Although the product was withdrawn in 2007, recent clinical studies report encouraging results on the beneficial effect of BAs-enriched extract supplements in reducing radiochemotherapy-induced cerebral edema in patients affected by primary or secondary malignant cerebral tumors (127-128). This positive role can be attributed to the anti-inflammatory activity of AKBA.

BOSWELLIA IN SKIN DISORDERS

Thanks to its multitarget effect, boswellia has also found application in the treatment of skin diseases characterized by an immune response. Although there is currently little evidence, some results are encouraging in the application of boswellia to alleviate symptoms typical of inflammatory skin disorders.

Clinical evidence

Clinical studies evaluating the use of topical *B. serrata* are limited and heterogeneous. One study evaluated the application of a cream con-

taining 0.5% of BAs from a commercial preparation (5-Loxin®) on the photodamaged face of 15 women. In this randomized, double-blind, placebo-controlled, split-face study, the formulation was applied once a day for 30 days. The cream was well tolerated and improved scores (Dover score) of photodamaged skin, by reducing fine wrinkles and roughness and by increasing thickness. Improvements remained stable at follow-up after 2 months (129). Another randomized, placebo-controlled, double-blind clinical study evaluated the efficacy of a topical cream containing 2% of Bosexil®, a phytosomal formulation of *B. serrata*, in eczematous and psoriatic lesions. A total of 10 patients with psoriatic lesions and 9 patients with dermatitis were evaluated in comparison with their respective controls (10 patients in placebo, for both conditions). Boswellia treatment, twice a day for 30 days, improved both psoriatic and eczematous lesions in 60% of patients, *versus* no improvement in the respective placebo groups (130). The same preparation was evaluated in radio-damaged skin. A total of 55 patients treated with radiotherapy for breast cancer (50 Gy dose) applied the cream twice a day (30 days) in comparison to 59 patients in the placebo group. The boswellia-containing cream reduced the intense form of erythema compared to the control group (22% *vs.* 49%) and decreased the use of topical cortisone in patients (25% *vs.* 63%) (131). Finally, a gel containing 2% of powdered *B. serrata* was evaluated in 95 women affected by vaginal candidiasis in an open clinical study. The patients applied the gel for 7 consecutive nights and the treatment decreased different symptoms compared to the previous baseline such as pain, itching, and secretion (<6% *vs.* >60% on average for all parameters). The effects were also confirmed by the measurement of oxidant and proapoptotic markers in vaginal discharge (132).

BOSWELLIA IN VETERINARY USE

B. serrata gum-resin and extracts are currently used as feed additives for cats and dogs (133-134), and as ingredients of dietary supplements for the maintenance and support of joint health and flexibility (135). Recently, a *B. serrata* extract, characterized by over 65% of BAs, max. 0.009% of methyleugenol and max. 0.028% of estragole, has been approved as a sensory additive in complete feed for horses and dogs (136). To evaluate the benefits arising from a diet supplementation with *B. serrata* products for joint health, different veterinary clinical trials in dogs and horses have been carried out, as detailed in Table 1. Among the nine trials highlighted in the literature search, seven were conducted in dogs (137-142) and two in horses (143-144). *B. serrata* products were usually administered with the meal and in multi-ingredient dietary supplements, containing other botanicals, such as *Curcuma longa* L., *Camellia sinensis* (L.) O. Kuntze, *Ribes nigrum* L., *Harpagophytum procumbens* DC, *Zingiber officinale* (L.) Rosc and *Ananas comosus* (L.) Merr., as well as other products such as glucosamine, chondroitin sulfate, fish oil, or cannabidiol), which are commonly exploited to support joint health and to relieve inflammation and pain (145-150). Although most studies (138-144) demonstrated favorable tolerability and overall benefits of the tested supplements in pain relief and reduction of clinical signs of osteoarthritis and joint inflammation (e.g., lameness, mobility, and joint swelling), the presence of multiple components does not allow to clarify the true contribution of the *B. serrata* extracts, which were often not defined or standardized (138, 140, 141, 143, 145). Only one veterinary clinical trial by Reichling *et al.* (136) evaluated the benefits of dietary supplementation with a standardized extract from *B. serrata* resin (extract BSB108, product of Bogar AG, Zürich), containing ≥50% of triterpenic acids, in dogs with inflammatory joint and spinal disease. The supplement, administered at 400 mg/10 kg body weight with the meal once daily for 6 weeks, led to overall benefits on joint function, with a reduction of lameness, local pain, and stiff gait starting from 2 weeks of treatment. The authors concluded that using a standardized extract in dietary supplementation of dogs may improve joint function and symptoms of osteoarthritis (136).

Table 1. Veterinary clinical trials on the effects of *Boswellia serrata* Roxb. ex Colebr. extracts in inflammatory diseases in dogs and horses.

Authors, year [Ref.]	Study Design	Species (years)/ n. (sex)/ disease	Treatment (Dosage) Duration	Product/ composition	Endpoints/ efficacy score	Outcomes	Adverse events
Reichling *et al.* 2004 (136)	OM, VCT	Dogs (2-16)/ 29 (males and females)/ inflammatory joint and spinal disease	BS resin extract (400 mg/ 10 kg body weight) once daily for 6 weeks with meal	BSB108 standardized extract from BS (Bogar AG, Zürich)/ ≥50% triterpenic acids	Severity of clinical signs, *i.e.* lameness, local pain and stiff gait (T0 and after 2, 4, and 6 weeks)/ 4 scale: very good, good, moderate or insufficient	Statistically significant overall efficacy starting from 2 weeks of treatment (score good or very good)	Reversible episodes of diarrhea and flatulence (suspected relationship with BSB108 in one case)
Martello *et al.* 2018 (137)	PO, VCT	Medium to large dogs (18 months to 10 years)/ 13 (males and females)/ osteoarthritis	Dietary supplement containing BS extract in association/ (2.0 gr of tablet, containing 31.5 mg BS, daily) once daily for 60 days	Dietary supplement (Candioli Pharma S.p.A, Italy)/ FLEXIDE® (*Camellia sinensis* (L.) O. Kuntze, BS olibanum, Copper complexes of chlorophylls E141), glucosamine (99% purity), chondroitin sulfate (low molecular weight, purity 100%), hyaluronic acid, collagen type II-not hydrolised	Clinical general examinations, orthopedic exam (lameness), blood test, pain (T0 and after 30 and 60 days)/ pain scale: 1 (mild) to 4 (severe); lameness scale: successful (no longer lame), improved (from T0 to T2), failure (unchanged or worsened)	Chronic orthopedic pain relief and reduction of clinical signs (84% improved lameness)	Lacking side effects and episodes of diarrhea or vomiting
Martello *et al.* 2019 (138)	Pilot study, VCT	Large dogs (5-14 years)/ 10 (males and females)/ osteoarthritis	Dietary supplement containing BS extract in association/ (2.0 gr of tablet, containing 31.5 mg BS, daily) once daily for 30 days	Dietary supplement (Candioli Pharma S.p.A, Italy)/ Cannabidiol (CBD), Casperome® (BS; >25% terpenic acids; Indena, Italy), industrial hemp oil and powdered melon fruit pulp and juice (Cucumis melo L.) extract	Veterinary evaluations and questionnaires of owners on chronic pain and palatability (T0 and after 15 and 30 days)	Significant improvement in pain management and mobility	Well tolerability and palatability; lacking episodes of vomiting or diarrheal
Musco *et al.* 2019 (139)	DB, VCT	Large dogs (5-14 years)/ 20 (males and females)/ osteoarthritis	Nutritional supplement containing BS extract in association/ 0.5 ml kg^{-1}, corresponding to about 2.1% BS extract, once daily for 90 days	Dìnamic™ (Dynamopet srl, Verone, Italy)/ Glucosamine sulphate 10%, Krill oil 3%, Chondroitine sulphate 1.25%, *Ribes nigrum*, Krill flour 1%, *Lentinus edodes*, *Equisetum arvense*, *Curcuma longa* L., BS extract, and *Harpagophytum procumbens* DC extracts	Blood analyses and a clinical examination for lameness, pain on manipulation and palpation, range of motion and joint swelling (T0 and after 30, 60 and 90 days)/ scale grade: 0 (none), 1 (slight), 2 (moderate) and 3 (severe)	Significant improvement of clinical signs (lameness, pain on manipulation and palpation, range of motion and joint swelling)	Well tolerability; lacking side effects
Caterino *et al.* 2021 (140)	R, PC, VCT	Dogs (>1 year)/ 20 (males and females)/ dysplasia and signs of osteoarthritis	Nutraceutical containing BS extract in association/ 1 tablet/ 10 kg of bodyweight for 90 days	Nutraceutical (Aurora Biofarma Milan, Italy)/ Glucosamine (GS), chondroitin sulfate, fish-oil (containing 80% of omega 3-fatty acid), vitamin C and E, saccharomyces Cerevisiae, boswellici acid and Curcuvet®	Orthopaedic (joint effusion, pain during manipulation, lameness) and neurologic examination and force plate gait analysis (T0 and after 45 and 90 days of treatment and after 60 days post-treatment)	Increasing values of ground reaction forces likely associated with pain reduction	Nr

Authors, year [Ref.]	Study Design	Species (years)/ n. (sex)/ disease	Treatment (Dosage) Duration	Product/ composition	Endpoints/ efficacy score	Outcomes	Adverse events
Gabriele *et al.*, 2022 (141)	R, PC, DB, VCT	Dogs (8-15 years)/20 (males and females)/ osteoarthritis	Food supplement containing 9.6% BS extract in association/ one tablet (2 gr)/10 kg of body weight, once daily for 150 days	Food supplement (Candioli Pharma Srl)/ *Cannabis sativa* oil, BS phospholipid (Indena SpA), *Zingiber officinale* extract, Vitamin C, appetite stimulants and technological additives, alfa-tocopherol	Serum inflammatory and oxidative stress biomarkers (T0 and after 20, 40, 60 and 80 days, and after 110, 140, and 170 days)	Significant reduction of inflammation and oxidative stress	Nr
Martello *et al.* 2022 (142)	R, PC, DB, VCT	Dogs (>6 months)/ 40 (males and females)/ osteoarthritis	one tablet (2 gr)/10 kg of body weight, once daily for six weeks	Food supplement (Confis Ultra, Candioli s.r.l., Italy)/ FLEXIDE® (Camellia sinensis (L.) O. Kuntze, BS olibanum, Copper complexes of chlorophylls E141), glucosamine (99% purity), chondroitin sulfate (low molecular weight, purity 100%), hyaluronic acid, collagen type II-not hydrolised, appetite stimulants	Clinical signs of OA progression, lameness and pain (T0 and after 40 and 60 days)	Significant improvement of clinical signs and pain lowering	Lacking adverse effects
Van de Water *et al.* 2016 (143)	R, B, VCT	Standardbred horses/24 (female)/healthy animals with experimentally induced synovitis by LPS injection	Multingredient supplement containing BS extract/ 45 mL twice per day for 28 days prior to articular challenge and during the 3-day test period	Cavalor ArtiTec Liquid Supplement (Nutriquine NV, Drongen, Belgium)/ glucosamine sulphate 2KCL, shark chondroitin sulphate sodium, MSM, boswellic acid dry extract 65%, *Ananasus comosus* extract 2500 GDU, L-glutamine, feverfew dry extract PE 4:1, hyaluronic acid	Clinical examinations for synovitis and lameness	Significant lowering of proinflammatory biomarkers in synovial fluid	Lacking side effects
Andrews *et al.* 2022 (144)	R, Crossover	Thoroughbred horses (3–20 years)/10 (geldings and mares)/ osteoarthritis	Multingredient supplement containing BS extract/ supplement mixed with grain administered each morning (56.7 g/daily)	BLP (Absorbine® Buteless® Performance pellets, W.F. Young Inc.)/ Longvida® optimised curcumin extract (Verdure Sciences), Omolene 100, Purina Mills LLC, *yucca schidigera*, vitamin B12, BS extract, methylsulfonylmethane, alfalfa and flaxseed meal, wheat middlings, lignin sulfonate, cold-pressed soybean oil and sodium propionate	Lameness examination, range of motion, pain on palpation and force platform data; serum biochemistry and gastric lesions	Improved weight bearing and force platform; lacking improvement in lameness scores and blood parameters alterations	Lacking gastric lesions

OM: open multi-centre; VCT: veterinary clinical trial; R: Randomized; B: Blinded; PO: prospective observational; BS: *Boswellia serrata* Roxb. ex Colebr.; t0: beginning of the study; DB: Double-Blind; PC: Placebo-Controlled. Nr: not report.

SAFETY OF B. SERRATA

Further toxicological reports on *B. serrata* are required to determine a comprehensive safety profile. Preclinical studies have shown that the acidic and non-acidic fractions of *B. serrata* gum resin extracts are non-irritating to the skin and eyes and, when consumed orally, did not induce mutagenesis, did not cause toxicity in the liver, kidneys, and stomach (151). When used as a flavoring agent, in complete feed for dogs and horses, they result safe at 330 mg/kg and 100 mg/kg, respectively. No conclusion can be yet drawn on its potential to be a respiratory sensitizer (152). The LD_{50} of BAs is >2 g/kg in rats and mice when administered orally or intraperitoneally. Subacute toxicity studies (3 months) in rabbits and chronic toxicity studies (over six months) in rats and monkeys have found no toxic effects of BAs at high doses (153). These data could support the safety of the human oral ingestion of *B. serrata* when consumed at a dose not greater than 167 mg per kg body weight (151).

In clinical practice, oral doses of 200-400 mg are often standardized to contain 37.5% of BAs per dose, while some commercial sources may contain up to 65% of BAs (153). Boswellia appears to be safe in humans and no significant adverse effects were observed in the majority of clinical trials (154). In general, side effects are mild and transient and affect the gastrointestinal tract (nausea, hyperacidity with reflux, and epigastric pain) (153).

The safety of boswellia in children or during pregnancy and breastfeeding cannot be recommended, because it has not been specifically studied. Notably, boswellia seems to have emmenagogue properties and may mask asthma in pediatric care (153).

Herb-drug or herb-nutrient interactions should also be considered with boswellia. Boswellia may be responsible for pharmacodynamic interactions, as it potentiates the effects of anti-neoplastic agents (as it inhibits cell proliferation), the activity of warfarin (because it inhibits lipoxygenase and interacts with COX-1), and the activity of pharmaceutical leukotriene inhibitors (as AKBA inhibits 5-LOX) (153, 155). Moreover, boswellia may impair the absorption of lipid-soluble medications and could lead to pharmacokinetic interactions as the potential inhibition of CYP3A4, CYP2C9, CYP2C19, and glycoprotein P as evidenced by *in vitro* studies (155). Finally, although it is not reported in the literature, it is plausible that after BAs administration, a bile acid sequestering activity may occur to some extent, leading to liver fatigue, especially in combination with herbal products and/or drugs with a choleretic or cholagogue effect. An example could be represented by the association of boswellia and turmeric in multi-component products (153, 156). In this context, boswellia has been implicated in liver injury, when included in multi-ingredient dietary supplements, but a specific contribution of boswellia to the hepatic toxicity could not be established (157).

In conclusion, *B. serrata* appears to be safe in and of itself, but in association with other plants or drugs could be responsible for serious adverse interactions that can endanger the health of users.

CONCLUSIONS

Taken together, the clinical and preclinical evidence suggest that boswellia is a medicinal plant endowed with pleiotropic beneficial effects, especially in the application of treatment for inflammatory diseases. These effects are largely attributed to the pharmacology of BAs. There are a plethora of clinical studies examining the use of boswellia in the treatment of asthma, skin, intestinal, and osteoarticular inflammatory diseases. On the other hand, mainly preclinical studies are available for the use of boswellia in cardiovascular and neurodegenerative diseases, and in cancer. For these conditions, further studies are warranted. Moreover, given their pharmacological importance, an accurate quantification of BAs within the extracts used in future studies is also recommended. Besides medicinal use, an interesting application is represented by the production of

animal food with *B. serrata* as an additive. Despite these interesting and healthy properties, the pharmacokinetic profile may represent the major limit, having a low permeability through biological membranes with consequent poor bioavailability. This problem represents a limiting factor that affects the clinical effectiveness of treatment with boswellia extracts. In this regard, the increase in the permeability of AKBA through biological membranes is the objective of various studies currently underway, and the main line of upgrade is the study of innovative formulation technologies using cyclodextrin and poloxamer solid dispersion systems (158). Indeed, the cyclodextrins in these formulations allow increasing the permeability of intestinal cells to absorb BAs, while the poloxamer promotes better solubility of AKBA, leading to enhanced absorption. In this context, we previously cited Casperome®, a BAs formulation composed of a lecithin-based delivery system for the treatment of UC. Ongoing research on innovative formulation technologies holds promise for improving the bioavailability and clinical efficacy of BAs, and future studies may explore additional applications of this versatile natural remedy.

In conclusion, while further human clinical studies are needed to strengthen the preclinical evidence, *B. serrata* undoubtedly appears to be a promising medicinal plant, useful as a remedy for a plethora of inflammatory conditions. Furthermore, its toxicological profile is favorable, particularly when used alone and not in multi-ingredient products or in combination with other therapies.

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REFERENCES

1. Tulin M, Wharfa AM. The Frankincense Trees (Boswellia spp., Burseraceae) of Northern Somalia and Southern Arabia. Kew Bulletin. 1987;42(3):487-500.
2. World Health Organization. WHO Monographs on Selected Medicinal Plants, 2009, Vol. 4, Geneva, WHO press. Available from: xxxxxxxxx. Accessed: xxxxxxxxx
3. Ph.Eur. 2022: European Pharmacopoeia. 11th edition. Strasbourg (FR): Directorate for the Quality of Medicines and HealthCare of the Council of Europe (EDQM); 2022. Available from: xxxxxxxxx. Accessed: xxxxxxxxx
4. Miran M, Amirshahrokhi K, Ajanii Y, Zadali R, Rutter MW, Enayati A, et al. Taxonomical Investigation, Chemical Composition, Traditional Use in Medicine, and Pharmacological Activities of Boswellia sacra Flueck. Evid Based Complement Alternat Med. 2022;2022:8779676. doi: 10.1155/2022/8779676.
5. Abdel-Tawab M, Werz O, Schubert-Zsilavecz M. Boswellia serrata: an overall assessment of in vitro, preclinical, pharmacokinetic and clinical data. Clin Pharmacokinet. 2011;50(6):349-69. doi: 10.2165/11586800-000000000-00000.
6. Al-Harrasi A, Rehman NU, Khan AL, Al-Broumi M, Al-Amri I, Hussain J, et al. molecular and structural studies of Bo-

swellia species: β-Boswellic Aldehyde and 3-epi-11β-Dihydroxy BA as precursors in biosynthesis of boswellic acids. PLoS One. 2018;13(6):e0198666. doi: 10.1371/journal.pone.0198666.
7. Mannino G, Occhipinti A, Maffei ME. Quantitative Determination of 3-O-Acetyl-11-Keto-βBoswellic Acid (AKBA) and Other Boswellic Acids in Boswellia sacra Flueck (syn. B. carteri Birdw) and Boswellia serrata Roxb. Molecules. 2016;21(10):1329. doi: 10.3390/molecules21101329.
8. Iram F, Khan SA, Husain A. Phytochemistry and potential therapeutic actions of Boswellic acids: A mini-review. Asian Pac J Trop Biomed. 2017; 7(6):513-23. doi: 10.1016/j.apjtb.2017.05.001.
9. EMEA/COMP/2247/02 Available from: https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/02/117-public-summary-positive-opinion-orphan-designation-boswellia-serrata-resin-extract-treatment_en.pdf. Accessed: Aug 25, 2023.
10. Biagi M, Pecorari R, Appendino G, Miraldi E, Magnano AR, Governa P, et al. Herbal Products in Italy: The Thin Line between Phytotherapy, Nutrition and Parapharmaceuticals; A Normative Overview of the Fastest Growing Market in Europe. Pharmaceuticals. 2016;9(4):65. doi: 10.3390/ph9040065.
11. Italian Health Minister DM 10/08/2018, attachment 1. Available from: https://www.gazzettaufficiale.it/eli/id/2018/09/26/18A06095/sg with subsequent modifications: https://www.salute.gov.it/portale/temi/allegato_decreto_botanicals.pdf. Accessed: Aug 24, 2023.
12. Zwerger M, Ganzera M. Analysis of boswellic acids in dietary supplements containing Indian frankincense (Boswellia serrata) by Supercritical Fluid Chromatography. J Pharm Biomed Anal. 2021;201:114106. doi: 10.1016/j.jpba.2021.114106.
13. Governa P, Marchi M, Cocetta V, De Leo B, Saunders PTK, Catanzaro D, et al. Effects of Boswellia Serrata Roxb. and Curcuma longa L. in an In Vitro Intestinal Inflammation Model Using Immune Cells and Caco-2. Pharmaceuticals. 2018;11(4):126. doi: 10.3390/ph11040126.
14. Ammon HP. Boswellic acids in chronic inflammatory diseases. Planta Med. 2006 Oct;72(12):1100-16. doi: 10.1055/s-2006-947227.
15. Poeckel D, Werz O. Boswellic acids: biological actions and molecular targets. Curr Med Chem. 2006;13(28):3359-69. doi: 10.2174/092986706779010333.
16. Siddhu NSS, Guru A, Satish Kumar RC, Almutairi BO, Almutairi MH, Juliet A, et al. Pro-inflammatory cytokine molecules from Boswellia serrate suppresses lipopolysaccharides induced inflammation demonstrated in an in-vivo zebrafish larval model. Mol Biol Rep. 2022 Aug;49(8):7425-35. doi: 10.1007/s11033-022-07544-5.
17. Giresha AS, Urs D, Manjunatha JG, Sophiya P, Supreetha BH, Jayarama S, et al. Group IIA secreted phospholipase A2 inhibition by elemolic acid as a function of anti-inflammatory activity. Sci Rep. 2022 May 10;12(1):7649. doi: 10.1038/s41598-022-10950-1.
18. Takada Y, Ichikawa H, Badmaev V, Aggarwal BB. Acetyl-11-keto-beta-boswellic acid potentiates apoptosis, inhibits invasion, and abolishes osteoclastogenesis by suppressing NF-kappa B and NF-kappa B-regulated gene expression. J Immunol. 2006 Mar 1;176(5):3127-40. doi: 10.4049/jimmunol.
19. Barakat BM, Ahmed HI, Bahr HI, Elbahaie AM. Protective Effect of Boswellic Acids against Doxorubicin-Induced Hepatotoxicity: Impact on Nrf2/HO-1 Defense Pathway. Oxid Med Cell Longev. 2018 Feb 6;2018:8296451. doi: 10.1155/2018/8296451.
20. Khan A, Khan I, Halim SA, Rehman NU, Karim N, Ahmad W, et al. Anti-diabetic potential of β-boswellic acid and 11-ke-

to-β-boswellic acid: Mechanistic insights from computational and biochemical approaches. Biomed Pharmacother. 2022 Mar;147:112669. doi: 10.1016/j.biopha.2022.112669.
21. Rajabian A, Farzanehfar M, Hosseini H, Arab FL, Nikkhah A. Boswellic acids as promising agents for the management of brain diseases. Life Sci. 2023 Jan 1;312:121196. doi: 10.1016/j.lfs.2022.121196.
22. Shadfar S, Khanal S, Bohara G, Kim G, Sadigh-Eteghad S, Ghavami S, et al. Methanolic Extract of Boswellia serrata Gum Protects the Nigral Dopaminergic Neurons from Rotenone-Induced Neurotoxicity. Mol Neurobiol. 2022 Sep;59(9):5874-90. doi: 10.1007/s12035-022-02943-y.
23. Shasaltaneh MD, Naghdi N, Ramezani S, Alizadeh L, Riazi GH. Protection of Beta Boswellic Acid against Streptozotocin-induced Alzheimer's Model by Reduction of Tau Phosphorylation Level and Enhancement of Reelin Expression. Planta Med. 2022 Apr;88(5):367-79. doi: 10.1055/a-1502-7083.
24. Al-Yasiry AR, Kiczorowska B. Frankincense--therapeutic properties. Postepy Hig Med Dosw (Online). 2016 Jan 4;70:380-91. doi: 10.5604/17322693.1200553.
25. Jaroš P, Timkina E, Michailidu J, Maršík D, Kulišová M, Kolouchová I, et al. Boswellic Acids as Effective Antibacterial Antibiofilm Agents. Molecules. 2022 Jun 13;27(12):3795. doi: 10.3390/molecules27123795.
26. Raina D, Khan FG, Tiwari H, Sangwan PL, Nargotra A, Kumar V, et al. Boswellic acids, as novel inhibitor targeting peptidoglycan biosynthetic enzyme UDP-N-acetylglucosamine enolpyruvyl transferase (MurA) in Escherichia coli. Arch Microbiol. 2022 Jul 12;204(8):472. doi: 10.1007/s00203-022-03066-7.
27. Gupta M, Kumar S, Kumar R, Kumar A, Verma R, Darokar MP, et al. Inhibition of heme detoxification pathway in malaria parasite by 3-hydroxy-11-keto-β-boswellic acid isolated from Boswellia serrata. Biomed Pharmacother. 2021 Dec;144:112302. doi: 10.1016/j.biopha.2021.112302.
28. Caliebe RH, Scior T, Ammon HPT. Binding of boswellic acids to functional proteins of the SARS-CoV-2 virus: Bioinformatic studies. Arch Pharm (Weinheim). 2021 Nov;354(11):e2100160. doi: 10.1002/ardp.202100160.
29. Ammon HP. Boswellic acids in chronic inflammatory diseases. Planta Med. 2006;72(12):1100-16. doi: 10.1055/s-2006-947227.
30. Ammon HP. Modulation of the immune system by Boswellia serrata extracts and boswellic acids. Phytomedicine. 2010 Sep;17(11):862-7. doi: 10.1016/j.phymed.2010.03.003.
31. Poeckel D, Werz O. Boswellic acids: biological actions and molecular targets. Curr Med Chem. 2006;13(28):3359-69. doi: 10.2174/092986706779010333.
32. Sengupta K, Golakoti T, Marasetti AK, Tummala T, Ravada SR, Krishnaraju AV, et al. Inhibition of TNFα production and blocking of mitogen-activated protein kinase/ NFκB activation in lipopolysaccharide-induced THP-1 human monocytes by 3-O-acetyl-11-keto-β-boswellic acid. J Food Lipids. 2009;16(3):325-44. doi: 10.1111/j.1745-4522.2009.01150.x.
33. Gilbert NC, Gerstmeier J, Schexnaydre EE, Börner F, Garscha U, Neau DB, et al. Structural and mechanistic insights into 5-lipoxygenase inhibition by natural products. Nat Chem Biol. 2020 Jul;16(7):783-790. doi: 10.1038/s41589-020-0544-7.
34. Soni KK, Meshram D, Lawal TO, Patel U, Mahady GB. Fractions of Boswellia Serrata Suppress LTA4, LTC4, Cyclooxygenase-2 Activities and mRNA in HL-60 Cells and Reduce Lung Inflammation in BALB/c Mice. Curr Drug Discov Technol. 2021;18(1):95-104. doi: 10.2174/1570163817666200127112928.

35. Liu Z, Liu X, Sang L, Liu H, Xu Q, Liu Z. Boswellic acid attenuates asthma phenotypes by downregulation of GATA3 via pSTAT6 inhibition in a murine model of asthma. Int J Clin Exp Pathol. 2015 Jan 1;8(1):236-43.
36. Zhou X, Cai J, Zhu W, Zhao H, Wang K, Zhang X. Zhou X, Cai JG, Zhu WW, Zhao HY, Wang K, Zhang XF. Boswellic acid attenuates asthma phenotype by downregulation of GATA3 via nhibition of PSTAT6. Genet Mol Res. 2015 Jul 6;14(3):7463-8.
37. Houssen ME, Ragab A, Mesbah A, El-Samanoudy AZ, Othman G, Moustafa AF, et al. Natural anti-inflammatory products and leukotriene inhibitors as complementary therapy for bronchial asthma. Clin Biochem. 2010 Jul;43(10-11):887-90. doi: 10.1016/j.clinbiochem.2010.04.061.
38. Al-Jawad FH, Al-Razzuqi RA, Hashim HM, Al-Bayati NJ. Glycyrrhiza glabra versus Boswellia carterii in chronic bronchial asthma: A comparative study of efficacy. Ind Journal of Allergy, Asthma and Immunology. 2012;26(1):6. doi: 10.4103/0972-6691.104437
39. Gupta I, Gupta V, Parihar A, Gupta S, Lüdtke R, Safayhi H, et al. Effects of Boswellia serrata gum resin in patients with bronchial asthma: results of a double-blind, placebo-controlled, 6-week clinical study. Eur J Med Res. 1998 Nov 17;3(11):511-4.
40. Ferrara T, De Vincentiis G, Di Pierro F. Functional study on Boswellia phytosome as complementary intervention in asthmatic patients. Eur Rev Med Pharmacol Sci. 2015 Oct;19(19):3757-62.
41. Badria FA, Mohammed EA, El-Badrawy MK, El-Desouky M. Natural leukotriene inhibitor from Boswellia: a potential new alternative for treating bronchial asthma. Alternative & Complementary Ther. 2004;10(5):257-65.
42. Xia Y, Kelton CM, Xue L, Guo JJ, Bian B, Wigle PR. Safety of long-acting beta agonists and inhaled corticosteroids in children and adolescents with asthma. Ther Adv Drug Saf. 2013 Dec;4(6):254-63. doi: 10.1177/2042098613504124.
43. Yugandhar P, Rao KM, Sengupta K. A novel herbal composition containing extracts of Boswellia serrata gum resin and Aegle marmelos fruit alleviates symptoms of asthma in a placebo controlled double-blind clinical study. Phytother Res. 2018 Jan;32(1):140-150. doi: 10.1002/ptr.5963.
44. Roy NK, Parama D, Banik K, Bordoloi D, Devi AK, Thakur KK, et al. An Update on Pharmacological Potential of Boswellic Acids against Chronic Diseases. Int J Mol Sci. 2019;20(17):4101. doi: 10.3390/ijms20174101.
45. Ammon HPT. Boswellic Acids and Their Role in Chronic Inflammatory Diseases. Adv Exp Med Biol. 2016;928:291-327. doi: 10.1007/978-3-319-41334-1_13.
46. In vitro Antioxidant Activity and Anti Inflammatory Activity of Methanolic Leaf Extract of Boswellia serrata. IJLBPR. 2012;1(4). Available from: http://www.ijlbpr.com/index.php?m=content&c=index&a=show&catid=117&id=432. Accessed: Jan 29, 2023.
47. Catanzaro D, Rancan S, Orso G, Dall'Acqua S, Brun P, Giron MC, et al. Boswellia Serrata Preserves Intestinal Epithelial Barrier from Oxidative and Inflammatory Damage. PLOS ONE. 2015;10(5): e0125375. doi: 10.1371/journal.pone.0125375.
48. Moussaieff, A, Mechoulam R. Boswellia Resin: From Religious Ceremonies to Medical Uses; a Review of in-Vitro, in-Vivo and Clinical Trials. J Pharm Pharmacol. 2009;61(10):1281-93. doi: 10.1211/jpp/61.10.0003.
49. Riva A, Giacomelli L, Togni S, Franceschi F, Eggenhoffner R, Zuccarini MC, et al. Oral Administration of a Lecithin-Based Delivery Form of Boswellic Acids (Casperome®) for the Prevention of Symptoms of Irritable Bowel Syndrome: A Randomized Clinical Study. Minerva Gastroenter-

ol Dietol. 2019;65(1):30-5. doi: 10.23736/S1121-421X.18.02530-8.
50. Pellegrini L, Milano E, Franceschi F, Belcaro G, Gizzi G, Feragalli B, et al. Managing ulcerative colitis in remission phase: usefulness of Casperome®, an innovative lecithin-based delivery system of Boswellia serrata extract. Eur Rev Med Pharmacol Sci. 2016 Jun;20(12):2695-700.
51. Gerhardt H, Seifert F, Buvari P, Vogelsang H, Repges R. Therapy of active Crohn disease with Boswellia serrata extract H 15. Z Gastroenterol. 2001;39(1):11-7. doi: 10.1055/s-2001-10708.
52. Holtmeier W, Zeuzem S, Preiss J, Kruis W, Böhm S, Maaser C, Raedler A, et al. Randomized, Placebo-Controlled, Double-Blind Trial of Boswellia Serrata in Maintaining Remission of Crohn's Disease: Good Safety Profile but Lack of Efficacy. Inflamm Bowel Dis. 2011;17(2):573-82. doi: 10.1002/ibd.21345.
53. Yu G, Xiang W, Zhang T, Zeng L, Yang K, Li, J. Effectiveness of Boswellia and Boswellia Extract for Osteoarthritis Patients: A Systematic Review and Meta-Analysis. BMC Complement Med Ther. 2020;20:225. doi: 10.1186/s12906-020-02985-6.
54. Kimmatkar N, Thawani V, Hingorani L, Khiyani R. Efficacy and Tolerability of Boswellia Serrata Extract in Treatment of Osteoarthritis of Knee – A Randomized Double Blind Placebo Controlled Trial. Phytomedicine. 2003;10(1):3-7. doi: 10.1078/094471103321648593.
55. Gupta PK, Samarakoon SMS, Chandola HM, Ravishankar B. Clinical evaluation of Boswellia serrata (Shallaki) resin in the management of Sandhivata (osteoarthritis). Ayu. 2011 Oct;32(4):478-82. doi: 10.4103/0974-8520.96119.
56. Shin MR, Kim HY, Choi HY, Park KS, Choi HJ, Roh SS. Boswellia serrata Extract, 5-Loxin®, Prevents Joint Pain and Cartilage Degeneration in a Rat Model of Osteoarthritis through Inhibition of Inflammatory Responses and Restoration of Matrix Homeostasis. Evid Based Complement Alternat Med. 2022 Oct 19;2022:3067526. doi: 10.1155/2022/3067526.
57. Karlapudi V, Sunkara KB, Konda PR, Sarma KV, Rokkam MP. Efficacy and Safety of Aflapin®, a Novel Boswellia Serrata Extract, in the Treatment of Osteoarthritis of the Knee: A Short-Term 30-Day Randomized, Double-Blind, Placebo-Controlled Clinical Study. J Am Nutr Assoc. 2023;42(2):159-68. doi:10.1080/07315724.2021.2014370.
58. Sengupta K, Alluri KV, Satish AR, Mishra S, Golakoti T, Sarma KV, et al. A Double Blind, A double blind, randomized, placebo-controlled study of the efficacy and safety of 5-Loxin for treatment of osteoarthritis of the knee. Arthritis Res Ther. 2008;10(4):R85. doi: 10.1186/ar2461.
59. Sengupta K, Krishnaraju AV, Vishal AA, Mishra A, Trimurtulu G, Sarma KV, et al. Comparative Efficacy and Tolerability of 5-Loxin® and Aflapin® Against Osteoarthritis of the Knee: A Double Blind, Randomized, Placebo Controlled Clinical Study. Int J Med Sci. 2010;7(6):366-77. doi: 10.7150/ijms.7.366.
60. Majeed M, Majeed S, Narayanan NK, Nagabhushanam K. A Pilot, Randomized, Double-Blind, Placebo-Controlled Trial to Assess the Safety and Efficacy of a Novel Boswellia Serrata Extract in the Management of Osteoarthritis of the Knee. Phytother Res. 2019;33(5):1457-68. doi: 10.1002/ptr.6338.
61. Naveed M, Majeed F, Taleb A, Zubair HM, Shumzaid M, Farooq MA, et al. A Review of Medicinal Plants in Cardiovascular Disorders: Benefits and Risks. Am J Chin Med. 2020;48(2):259-86. doi: 10.1142/S0192415X20500147.
62. Wang M, Chen M, Ding Y, Zhu Z, Zhang Y, Wei P, et al. Pretreatment with β-Boswellic Acid Improves Blood Stasis Induced Endothelial Dysfunction: Role of eNOS Activation. Sci Rep. 2015;5:15357. doi: 10.1038/srep15357.

63. Kokkiripati PK, Bhakshu LM, Marri S, Padmasree K, Row AT, Raghavendra AS, et al. Gum resin of Boswellia serrata inhibited human monocytic (THP-1) cell activation and platelet aggregation. J Ethnopharmacol. 2011;137(1):893-901. doi: 10.1016/j.jep.2011.07.004.
64. Roy S, Khanna S, Krishnaraju AV, Subbaraju GV, Yasmin T, Bagchi D, et al. Regulation of vascular responses to inflammation: inducible matrix metalloproteinase-3 expression in human microvascular endothelial cells is sensitive to antiinflammatory Boswellia. Antioxid Redox Signal. 2006;8(3-4):653-60. doi: 10.1089/ars.2006.8.653.
65. Bertocchi M, Isani G, Medici F, Andreani G, Tubon Usca I, Roncada P, et al. Anti-Inflammatory Activity of Boswellia serrata Extracts: An *In Vitro* Study on Porcine Aortic Endothelial Cells. Oxid Med Cell Longev. 2018 Jun 25;2018:2504305. doi: 10.1155/2018/2504305.
66. Taherzadeh D, Baradaran Rahimi V, Amiri H, Ehtiati S, Yahyazadeh R, Hashemy SI, et al. Acetyl-11-Keto-β-Boswellic Acid (AKBA) Prevents Lipopolysaccharide-Induced Inflammation and Cytotoxicity on H9C2 Cells. Evid Based Complement Alternat Med. 2022;2022:2620710. doi: 10.1155/2022/2620710.
67. Chen M, Wang M, Yang Q, Wang M, Wang Z, Zhu Y, et al. Antioxidant effects of hydroxysafflor yellow A and acetyl-11-keto-β- boswellic acid in combination on isoproterenol-induced myocardial injury in rats. Int J Mol Med. 2016;37(6):1501-10. doi: 10.3892/ijmm.2016.2571.
68. Baram SM, Karima S, Shateri S, Tafakhori A, Fotouhi A, Lima BS, et al. Functional improvement and immune-inflammatory cytokines profile of ischaemic stroke patients after treatment with boswellic acids: a randomized, double-blind, placebo-controlled, pilot trial. Inflammopharmacology. 2019;27(6):1101-12. doi: 10.1007/s10787-019-00627-z.
69. Li JY, Kampp JT. Review of Common Alternative Herbal "Remedies" for Skin Cancer. Dermatol Surg. 2019;45(1):58-67. doi: 10.1097/DSS.0000000000001622.
70. Hussain H, Ali I, Wang D, Hakkim FL, Westermann B, Rashan L, et al. Boswellic acids: privileged structures to develop lead compounds for anticancer drug discovery. Expert Opin Drug Discov. 2021 Aug;16(8):851-867. doi: 10.1080/17460441.2021.1892640.
71. Schmiech M, Ulrich J, Lang SJ, Büchele B, Paetz C, St-Gelais A, et al. 11-Keto-α-Boswellic Acid, a Novel Triterpenoid from Boswellia spp. with Chemotaxonomic Potential and Antitumor Activity against Triple-Negative Breast Cancer Cells. Molecules. 2021 Jan 12;26(2):366. doi: 10.3390/molecules26020366.
72. Mazzio EA, Lewis CA, Soliman KF. Transcriptomic Profiling of MDA-MB-231 Cells Exposed to Boswellia Serrata and 3-O-Acetyl-B-Boswellic Acid; ER/UPR Mediated Programmed Cell Death. Cancer Genomics Proteomics. 2017 Nov-Dec;14(6):409-25. doi: 10.21873/cgp.20051.
73. Li W, Liu J, Fu W, Zheng X, Ren L, Liu S, et al. 3-O-acetyl-11-keto-β-boswellic acid exerts anti-tumor effects in glioblastoma by arresting cell cycle at G2/M phase. J Exp Clin Cancer Res. 2018 Jul 3;37(1):132. doi: 10.1186/s13046-018-0805-4. Erratum in: J Exp Clin Cancer Res. 2022 Aug 3;41(1):236.
74. Park YS, Lee JH, Harwalkar JA, Bondar J, Safayhi H, Golubic M. Acetyl-11-keto-beta-boswellic acid (AKBA) is cytotoxic for meningioma cells and inhibits phosphorylation of the extracellular-signal regulated kinase 1 and 2. Adv Exp Med Biol. 2002;507:387-93. doi: 10.1007/978-1-4615-0193-0_60.
75. Roy NK, Parama D, Banik K, Bordoloi D, Devi AK, Thakur KK, et al. An update on pharmacological potential of boswellic acids against chronic diseases. Int J

Mol Sci. 2019;20(17):4101. doi: 10.3390/ijms20174101.
76. Feng Y, Zhang Q, Sun L. Five terpenoids from the gum resin of Boswellia carterii and their cytotoxicity. Fitoterapia. 2021;154:105017. doi: 10.1016/j.fitote.2021.105017.
77. Liu J-J, Nilsson A, Oredsson S, Badmaev V, Duan R-D. Keto-and acetyl-keto-boswellic acids inhibit proliferation and induce apoptosis in Hep G2 cells via a caspase-8 dependent pathway. In J Mol Med. 2002;10(4):501-5. Available from: https://www.spandidos-publications.com/ijmm/10/4/501. Accessed: Aug 26, 2023.
78. Lv M, Shao S, Zhang Q, Zhuang X, Qiao T. Acetyl-11-Keto-β-Boswellic acid exerts the anticancer effects via cell cycle arrest, apoptosis induction and autophagy suppression in non-small cell lung cancer cells. Onco Targets Ther. 2020;13:733-44. doi: 10.2147/OTT.S236346.
79. Efferth T, Oesch F. Anti-inflammatory and anti-cancer activities of frankincense: Targets, treatments and toxicities. Semin Cancer Biol. 2022;80:39-57. doi: 10.1016/j.semcancer.2020.01.015.
80. Khan MA, Ali R, Parveen R, Najmi AK, Ahmad S. Pharmacological evidences for cytotoxic and antitumor properties of Boswellic acids from Boswellia serrata. J Ethnopharmacol. 2016;191:315-23. doi: 10.1016/j.jep.2016.06.053.
81. Wang S, Wang H, Sun B, Li D, Wu J, Li J, et al. Acetyl-11-keto-β-boswellic acid triggers premature senescence via induction of DNA damage accompanied by impairment of DNA repair genes in hepatocellular carcinoma cells in vitro and in vivo. Fundam Clin Pharmacol. 2020;34(1):65-76. doi: 10.1111/fcp.12488.
82. Al-Bahlani S, Burney IA, Al-Dhahli B, Al-Kharusi S, Al-Kharousi F, Al-Kalbani A, et al. Boswellic acid sensitizes gastric cancer cells to Cisplatin-induced apoptosis via p53-mediated pathway. BMC Pharmacol Toxicol. 2020;21(1):64. doi: 10.1186/s40360-020-00442-1.
83. Sun MX, He XP, Huang PY, Qi Q, Sun WH, Liu GS, et al. Acetyl-11-keto-β-boswellic acid inhibits proliferation and induces apoptosis of gastric cancer cells through the phosphatase and tensin homolog / Akt/ cyclooxygenase-2 signaling pathway. World J Gastroenterol. 2020;26(38):5822-35. doi: 10.3748/wjg.v26.i38.5822.
84. Xia H, Wang CC, Wang RY, Liang NY, Wang XY, Song YL, et al. (One new cembranoid diterpene from gum resin of Boswellia carterii). Zhongguo Zhong Yao Za Zhi. 2021;46(9):2215-9. doi: 10.19540/j.cnki.cjcmm.20210115.602.
85. Sun X, Geng Y, Wang X, Qin D, Yu J. Cembrane-type diterpenoids from the gum resin of Boswellia carterii and their biological activities. RSC Adv. 2020;10(2):746-55. doi: 10.1039/c9ra09776g.
86. Conti S, Vexler A, Edry-Botzer L, Kalich-Philosoph L, Corn BW, Shtraus N, et al. Combined acetyl-11-keto-β-boswellic acid and radiation treatment inhibited glioblastoma tumor cells. PLoS One. 2018; 13(7):e0198627. doi: 10.1371/journal.pone.0198627.
87. Liu YQ, Wang SK, Xu QQ, Yuan HQ, Guo YX, Wang Q, et al. Acetyl-11-keto-β-boswellic acid suppresses docetaxel-resistant prostate cancer cells in vitro and in vivo by blocking Akt and Stat3 signaling, thus suppressing chemoresistant stem cell-like properties. Acta Pharmacol Sin. 2019; 40(5):689-98. doi: 10.1038/s41401-018-0157-9.
88. Jin L, Yingchun W, Zhujun S, Yinan W, Dongchen W, Hui Y, et al. 3-acetyl-11-keto-beta-boswellic acid decreases the malignancy of taxol resistant human ovarian cancer by inhibiting multidrug resistance (MDR) proteins function. Biomed Pharmacother. 2019;116:108992. doi: 10.1016/j.biopha.2019.108992.
89. Toden S, Okugawa Y, Buhrmann C, Nattamai D, Anguiano E, Baldwin N, Shakibaei M, Boland CR, Goel A. Novel Evidence for Curcumin and Boswellic Acid-Induced Chemoprevention through Regulation of

miR-34a and miR-27a in Colorectal Cancer. Cancer Prev Res. 2015;8(5):431-43. doi: 10.1158/1940-6207.CAPR-14-0354.

90. Yadav VR, Prasad S, Sung B, Gelovani JG, Guha S, Krishnan S, et al. Boswellic acid inhibits growth and metastasis of human colorectal cancer in orthotopic mouse model by downregulating inflammatory, proliferative, invasive and angiogenic biomarkers. Int J Cancer. 2012; 130(9):2176-84. doi: 10.1002/ijc.26251.
91. Liu HP, Gao ZH, Cui SX, Wang Y, Li BY, Lou HX, et al. Chemoprevention of intestinal adenomatous polyposis by acetyl-11-keto-beta-boswellic acid in APC(Min/+) mice. Int J Cancer. 2013;132(11):2667-81. doi: 10.1002/ijc.27929.
92. Chou YC, Suh JH, Wang Y, Pahwa M, Badmaev V, Ho CT, et al. Boswellia serrata resin extract alleviates azoxymethane (AOM)/dextran sodium sulfate (DSS)-induced colon tumorigenesis. Mol Nutr Food Res. 2017;61(9). doi: 10.1002/mnfr.201600984.
93. Sayed AS, Gomaa IEO, Bader M, el Sayed NSED. Role of 3-Acetyl-11-Keto-Beta-Boswellic Acid in Counteracting LPS-Induced Neuroinflammation via Modulation of miRNA-155. Mol Neurobiol. 2018;55:5798-808. doi: 10.1007/s12035-017-0801-2.
94. Marefati N, Beheshti F, Memarpour S, Rezaei M, Hosseini M. The effects of pre-treatment with olibanum and its constituent, boswellic acid on synaptic plasticity impairments induced by lipopolysaccharide in rats. Avicenna J Phytomed 2021;11:68. PMID: 33628721.
95. Shahidpour F, Mehrjerdi FZ, Mozayan MR, Marefati N, Hosseini M. The effects of frankincense extract on depression and anxiety-like behaviors induced by lipopolysaccharide in rats. Learn Motiv. 2021;73:101708. doi: 10.1016/J.LMOT.2021.101708.
96. Marefati N, Beheshti F, Memarpour S, Bayat R, Naser Shafei M, Sadeghnia HR, et al. The effects of acetyl-11-keto-β-boswellic acid on brain cytokines and memory impairment induced by lipopolysaccharide in rats. Cytokinez. 2020;131:155107. doi: 10.1016/J.CYTO.2020.155107.
97. Takada Y, Ichikawa H, Badmaev V, Aggarwal BB. Acetyl-11-Keto-β-Boswellic Acid Potentiates Apoptosis, Inhibits Invasion, and Abolishes Osteoclastogenesis by Suppressing NF-κB and NF-κB-Regulated Gene Expression. J Immunol. 2006;176:3127-40. doi: 10.4049/JIMMUNOL.176.5.3127.
98. Gomaa AA, Farghaly HA, Abdel-Wadood YA, Gomaa GA. Potential therapeutic effects of boswellic acids/Boswellia serrata extract in the prevention and therapy of type 2 diabetes and Alzheimer's disease. Naunyn Schmiedebergs Arch Pharmacol. 2021;394:2167-85. doi: 10.1007/s00210-021-02154-7.
99. Ahmed HH, Mohamed EM, El-Dsoki SM. Evidences for the promising therapeutic potential of boswellia serrata against alzheimer's disease: Pre-clinical study. Int J Pharm Pharm Sci 2014;6:384-92.
100. Wei C, Fan J, Sun X, Yao J, Guo Y, Zhou B, et al. Acetyl-11-keto-β-boswellic acid ameliorates cognitive deficits and reduces amyloid-β levels in APPswe/PS1dE9 mice through antioxidant and anti-inflammatory pathways. Free Radic Biol Med. 2020;150:96-108. doi: 10.1016/J.FREERADBIOMED.2020.02.022.
101. El-Magd MA, Khalifa SF, A Alzahrani FA, Badawy AA, El-Shetry ES, Dawood LM, et al. Incensole acetate prevents beta-amyloid-induced neurotoxicity in human olfactory bulb neural stem cells. Biomed Pharmacother. 2018;105:813-23. doi: 10.1016/j.biopha.2018.06.014.
102. Fathi E, Katouli FH, Riazi GH, Shasaltaneh MD, Parandavar E, Bayati S, et al. The Effects of Alpha Boswellic Acid on Reelin Expression and Tau Phosphorylation in Human Astrocytes. Neuromolecular Med. 2017;19:136-46. doi: 10.1007/s12017-016-8437-3.

103. Bakthira H, Awadh Ali NA, Arnold N, Teichert A, Wessjohann L. Anticholinesterase activity of endemic plant extracts from Soqotra. Afr J Tradit Complement Altern Med 2011;8:296-9. doi: 10.4314/ajtcam.v8i3.65292.
104. Morgese MG, Bove M, Francavilla M, Schiavone S, Dimonte S, Colia AL, et al. Sublingual AKBA Exerts Antidepressant Effects in the Aβ-Treated Mouse Model. Biomolecules. 2021;11(5):386. doi: 10.3390/BIOM11050686.
105. Rajabian A, Sadeghnia HR, Hosseini A, Mousavi SH, Boroushaki MT. 3-Acetyl-11-keto-β-boswellic acid attenuated oxidative glutamate toxicity in neuron-like cell lines by apoptosis inhibition. J Cell Biochem. 2020;121:1778-89. doi: 10.1002/jcb.29413.
106. Lu CW, Lin TY, Wang SJ. 11-Keto-β-Boswellic Acid Attenuates Glutamate Release and Kainic Acid-Induced Excitotoxicity in the Rat Hippocampus. Planta Med. 2020;86:434-41. doi: 10.1055/a-1107-9337.
107. Ding Y, Chen M, Wang M, Wang M, Zhang T, Park J, et al. Neuroprotection by acetyl-11-keto-β-Boswellic acid, in ischemic brain injury involves the Nrf2/HO-1 defense pathway. Sci Rep. 2014;4:7002. doi: 10.1038/srep07002.
108. Shadfar S, Khanal S, Bohara G, Kim G, Sadigh-Eteghad S, Ghavami S, et al. Methanolic Extract of Boswellia serrata Gum Protects the Nigral Dopaminergic Neurons from Rotenone-Induced Neurotoxicity. Mol Neurobiol. 2022;59(9):5874-90. doi: 10.1007/s12035-022-02943-y.
109. Doaee P, Rajaei Z, Roghani M, Alaei H, Kamalinejad M. Effects of Boswellia serrata resin extract on motor dysfunction and brain oxidative stress in an experimental model of Parkinson's disease. Avicenna J Phytomed 2019;9(3):281-90. PMID: 31143695.
110. Upadhayay S, Mehan S, Prajapati A, Sethi P, Suri M, Zawawi A, et al. Nrf2/HO-1 Signaling Stimulation through Acetyl-11-Keto-Beta-Boswellic Acid (AKBA) Provides Neuroprotection in Ethidium Bromide-Induced Experimental Model of Multiple Sclerosis. Genes. 2022;13(8):1324. https://doi.org/10.3390/genes13081324.
111. Minj E, Upadhayay S, Mehan S. Nrf2/HO-1 Signaling Activator Acetyl-11-keto-beta Boswellic Acid (AKBA)-Mediated Neuroprotection in Methyl Mercury-Induced Experimental Model of ALS. Neurochem Res. 2021;46(11):2867-84. doi: 10.1007/s11064-021-03366-2.
112. Karima O, Riazi G, Yousefi R, Movahedi AAM. The enhancement effect of beta-boswellic acid on hippocampal neurites outgrowth and branching (an in vitro study). Neurological Sciences 2010;31(3):315-20. doi: 10.1007/s10072-010-0220-x.
113. Mahmoudi A, Hosseini-Sharifabad A, Monsef-Esfahani HR, Yazdinejad AR, Khanavi M, Roghani A, et al. Evaluation of systemic administration of Boswellia papyrifera extracts on spatial memory retention in male rats. J Nat Med. 2011;65(3-4):519-25. doi: 10.1007/s11418-011-0533-y.
114. Sadeghi F, Khalaj-Kondori M, Hosseinpour Feizi MA, Shaikhzadeh Hesari F. The effect of aqueous extract of boswellia on spatial learning and memory in adult male rats. J Zanjan Univ Med Sci Health Serv. 2014;22.
115. Marefati N, Beheshti F, Mokhtari-Zaer A, Shafei MN, Salmani H, Sadeghnia HR, et al. The effects of Olibanum on oxidative stress indicators, cytokines, brain derived neurotrophic factor and memory in lipopolysaccharide challenged rats. Toxin Rev. 2022;41(1):129-42. doi: 10.1080/15569543.2020.1855653.
116. Khalaj-Kondori M, Sadeghi F, Hosseinpourfeizi MA, Shaikhzadeh-Hesari F, Nakhlband A, Rahmati-Yamchi M. Boswellia serrata gum resin aqueous extract upregulatesBDNF but not CREB expression in adult male rat hippocampus. Turk J Med Sci. 2016;46(5):1573-8. doi: 10.3906/sag-1503-43.
117. Adake P, Petimani MS, Kotian GB. Neurochemical Modulating Effect of Boswel-

lia serrata Roxb. ex Colebr: A Preclinical Research. Pharm Biomed Res. 2022;8:67-72. doi: 10.18502/PBR.V8I1.9389.
118. Adake P, Petimani MS, Jayaraj M, Rao SN. Preclinical evaluation of Boswellia serrata for anxiolytic activity. Int J Basic Clin Pharmacol. 2017;4:551-5. doi: 10.18203/2319-2003.IJBCP20150038.
119. Morgese MG, Bove M, Francavilla M, Schiavone S, Dimonte S, Colia AL, et al. Sublingual AKBA Exerts Antidepressant Effects in the Aβ-Treated Mouse Model. Biomolecules. 2021;11(5):686. https://doi.org/10.3390/BIOM11050686.
120. Meshkat S, Mahmoodi Baram S, Rajaei S, Mohammadian F, Kouhestani E, Amirzargar N, et al. Boswellia serrata extract shows cognitive benefits in a double-blind, randomized, placebo-controlled pilot clinical trial in individuals who suffered traumatic brain injury. Brain Inj. 2022;36(4):553-9. doi: 10.1080/02699052.2022.2059816.
121. Moein P, Abbasi Fard S, Asnaashari A, Baratian H, Barekatain M, Tavakoli N, et al. The effect of Boswellia Serrata on neurorecovery following diffuse axonal injury. Brain Inj. 2013;27(12):1454-60. doi: 10.3109/02699052.2013.825009.
122. Kamali H, Sedighi B, Pardakhty A, Shafiee K, Hasani BN. Effect of Boswellia papyrifera on cognitive impairment in multiple sclerosis. Iran J Neurol. 2014;13(3):149-53. PMID: 25422734.
123. Taghizadeh M, Maghaminejad F, Aghajani M, Rahmani M, Mahboubi M. The effect of tablet containing Boswellia serrata and Melisa officinalis extract on older adults' memory: A randomized controlled trial. Archives of Gerontology and Geriatrics 2018;75:146-50. doi: 10.1016/J.ARCHGER.2017.12.008.
124. Kirste S, Treier M, Wehrle SJ, Becker G, Abdel-Tawab M, Gerbeth K, et al. Boswellia serrata acts on cerebral edema in patients irradiated for brain tumors: a prospective, randomized, placebo-controlled, double-blind pilot trial. Cancer. 2011;117(16):3788-95. doi: 10.1002/cncr.25945.
125. Gerbeth K, Hüsch J, Fricker G, Werz O, Schubert-Zsilavecz M, Abdel-Tawab M. In vitro metabolism, permeation, and brain availability of six major boswellic acids from Boswellia serrata gum resins. Fitoterapia. 2013;84:99-106. doi: 10.1016/j.fitote.2012.10.009.
126. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu302117. Accessed: Aug 25, 2023.
127. Warnick RE. Treatment of adverse radiation effects with Boswellia serrata after failure of pentoxifylline and vitamin E: illustrative cases. J Neurosurg Case Lessons. 2023;5(5):CASE22488. doi: 10.3171/CASE22488.
128. Di Pierro F, Simonetti G, Petruzzi A, Bertuccioli A, Botta L, Bruzzone MG, et al. A novel lecithin-based delivery form of Boswellic acids as complementary treatment of radiochemotherapy-induced cerebral edema in patients with glioblastoma multiforme: a longitudinal pilot experience. J Neurosurg Sci. 2019;63(3):286-91. doi: 10.23736/S0390-5616.19.04662-9.
129. Pedretti A, Capezzera R, Zane C, Facchinetti E, Calzavara-Pinton P. Effects of topical boswellic acid on photo and age-damaged skin: clinical, biophysical, and echographic evaluations in a double-blind, randomized, split-face study. Planta Med. 2010;76(6):555-60. doi: 10.1055/s-0029-1240581.
130. Togni S, Maramaldi G, Di Pierro F, Biondi M. A cosmeceutical formulation based on boswellic acids for the treatment of erythematous eczema and psoriasis. Clin Cosmet Investig Dermatol. 2014;7:321-7. doi: 10.2147/CCID.S69240.
131. Togni S, Maramaldi G, Bonetta A, Giacomelli L, Di Pierro F. Clinical evaluation of safety and efficacy of Boswellia-based cream for prevention of adjuvant radiotherapy skin damage in mammary carcinoma: a randomized placebo-con-

trolled trial. Eur Rev Med Pharmacol Sci. 2015;19(8):1338-44. PMID: 25967706.
132. Moghadam FH, Tansaz M, Aminimoghaddam S, Hajimehdipoor H. The Effect of Boswellia Vaginal Gel on Oxidative Stress and Expression of Apoptotic Biomarkers in Vaginal Discharge of Women With Vaginitis. Res J Pharmacogn. 2022;9(2):29-36. doi: 10.22127/rjp.2021.299234.1763.
133. European Union. Register of Feed Additives pursuant to Regulation (EC) No 1831/2003 (2b natural products – botanically defined). Available from: https://food.ec.europa.eu/system/files/2022-01/animal-feed_additives_eu-register_1831-03_annex3e.pdf. Accessed: Aug 25, 2023.
134. EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP); Bampidis V, Azimonti G, Bastos ML, Christensen H, Fašmon Durjava M, et al. Scientific Opinion on the safety and efficacy of a feed additive consisting of an extract of olibanum from Boswellia serrata Roxb. ex Colebr. for use in dogs and horses (FEFANA asbl). EFSA J 2022; 20(3):e07158. doi: 10.2903/j.efsa.2022.7158.
135. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of health claims related to various food(s)/food constituent(s) claiming maintenance of joints (ID 1799, 1973, 2022, 2178, 2202, 2254, 2255, 2311, 2394, 2417, 2418, 2458, 2649, 2794, 2798, 3119, 3144, 3274, 3283, 3318, 3339, 3495, 3511, 3523, 3555, 3624, 3699, 3748, 3770, 3835, 3884, 3892, 3904, 3943, 3978, 4012, 4020, 4056, 4137, 4175), maintenance of bone (ID 1764, 1907, 2418, 4012, 4020, 4056, 4175) and maintenance of muscles (ID 2254, 2311) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA J 2010;8(2):1493.
136. Reichling J, Schmökel H, Fitzi J, Bucher S, Saller R. Dietary support with Boswellia resin in canine inflammatory joint and spinal disease. Schweiz Arch Tierheilkd. 2004;146(2):71-9. doi: 10.1024/0036-7281.146.2.71.
137. Martello E, Mauro B, Raffaella A, Biasibetti E, Dosio F, Daniela P, Natascia B. Evaluation of The Efficacy of a Dietary Supplement in Alleviating Symptoms in Dogs with Osteoarthritis. J Food Nutr 2018;4:1-8.
138. Martello EBM, Bisanzio D, Biasibetti E, Dosio F. Effects on Pain and Mobility of a New Diet Supplement in Dogs with Osteoarthritis: A Pilot Study. Ann Clin Lab Res. 2019;7(3):304. Available from: https://www.itmedicalteam.pl/articles/effects-on-pain-and-mobility-of-a-new-diet-supplement-in-dogs-with-osteoarthritis-a-pilot-study-102278.html. Accessed: Aug 26, 2023.
139. Musco N, Vassalotti G, Mastellone V, Cortese L, Della Rocca G, Molinari ML, et al. Effects of a nutritional supplement in dogs affected by osteoarthritis. Vet Med Sci. 2019;5(3):325-35. doi: 10.1002/vms3.182.
140. Caterino C, Aragosa F, Della Valle G, Costanza D, Lamagna F, Piscitelli A, et al. Clinical efficacy of Curcuvet and Boswellic acid combined with conventional nutraceutical product: An aid to canine osteoarthritis. PLoS One. 2021;16(5):e0252279. doi: 10.1371/journal.pone.0252279.
141. Gabriele V, Bisanzio D, Riva A, Meineri G, Adami R, Martello E. Long-term effects of a diet supplement containing Cannabis sativa oil and Boswellia serrata in dogs with osteoarthritis following physiotherapy treatments: a randomised, placebo-controlled and double-blind clinical trial. Nat Prod Res. 2022;37(11):1782-86. doi: 10.1080/14786419.2022.2119967.
142. Martello E, Bigliati M, Adami R, Biasibetti E, Bisanzio D, Meineri G, et al. Efficacy of a dietary supplement in dogs with osteoarthritis: A randomized placebo-controlled, double-blind clinical trial. PLoS One. 2022;17(2):e0263971. doi: 10.1371/journal.pone.0263971.
143. van de Water E, Oosterlinck M, Dumoulin M, van de Water E, Oosterlinck M, Dumoulin M, Korthagen NM, van Weeren PR, van den Broek J, et al. The preventive effects of two nutraceuticals on experimen-

tally induced acute synovitis. Equine Vet J. 2017;49(4):532-8. doi: 10.1111/evj.12629.
144. Andrews FM, Riggs LM, Lopez MJ, Keowen ML, Garza F, Takawira C, et al. Effect of an oral supplement containing curcumin extract (Longvida®) on lameness due to osteoarthritis and gastric ulcer scores. Equine Vet Educ. 2022;34(12):e591-e602. doi: 10.1111/eve.13616.
145. Barbeau-Grégoire M, Otis C, Cournoyer A, Moreau M, Lussier B, Troncy E. A 2022 Systematic Review and Meta-Analysis of Enriched Therapeutic Diets and Nutraceuticals in Canine and Feline Osteoarthritis. Int J Mol Sci. 2022;23(18):10384. doi: 10.3390/ijms231810384.
146. Mu P, Feng J, Hu Y, Xiong F, Ma X, Tian L. Botanical Drug Extracts Combined With Biomaterial Carriers for Osteoarthritis Cartilage Degeneration Treatment: A Review of 10 Years of Research. Front Pharmacol. 2022;12:789311. doi: 10.3389/fphar.2021.789311.
147. Chakraborty AJ, Mitra S, Tallei TE, Tareq AM, Nainu F, Cicia D, et al. Bromelain a Potential Bioactive Compound: A Comprehensive Overview from a Pharmacological Perspective. Life. 2021;11(4):317. doi: 10.3390/life11040317.
148. Dragos D, Gilca M, Gaman L, Vlad A, Iosif L, Stoian I, et al. Phytomedicine in Joint Disorders. Phytomedicine in Joint Disorders. Nutrients. 2017;9(1):70. doi: 10.3390/nu9010070.
149. Lima TM, Santiago NR, Alves ECR, Chaves DSA, Visacri MB. Use of cannabis in the treatment of animals: a systematic review of randomized clinical trials. Anim Health Res Rev. 2022;23(1):25-38. doi: 10.1017/S1466252321000189.
150. Cortez RE, Gonzalez de Mejia E. Blackcurrants (Ribes nigrum): A Review on Chemistry, Processing, and Health Benefits. J Food Sci. 2019;84(9):2387-401. doi: 10.1111/1750-3841.14781.
151. Alluri VK, Dodda S, Kilari EK, Golakoti T, Sengupta K. Toxicological Assessment of a Standardized Boswellia serrata Gum Resin Extract. Int J Toxicol. 2019;38(5):423-35. doi: 10.1177/1091581819858069.
152. European Food Safety Authority (EFSA). Safety and efficacy of a feed additive consisting of an extract of olibanum from Boswellia serrata Roxb. ex Colebr. for use in dogs and horses (FEFANA asbl). EFSA Journal 2022;20(3):e7158. doi: 10.2903/j.efsa.2022.7158.
153. Basch E, Boon H, Davies-Heerema T, Foppo I, Hashmi S, Hasskarl J, et al. Boswellia: an evidence-based systematic review by the Natural Standard Research Collaboration. J Herb Pharmacother. 2004;4(3):63-83. PMID: 15829470.
154. Karlapudi V, Sunkara KB, Konda PR, Sarma KV, Rokkam MP. Efficacy and Safety of Aflapin®, a Novel Boswellia Serrata Extract, in the Treatment of Osteoarthritis of the Knee: A Short-Term 30-Day Randomized, Double-Blind, Placebo-Controlled Clinical Study. J Am Nutr Assoc. 2023;42(2):159-168. doi: 10.1080/07315724.2021.2014370.
155. Şen A. Complementary medicines used in ulcerative colitis and unintended interactions with cytochrome P450-dependent drug-metabolizing enzymes. Turk J Med Sci. 2022;52(5):1425-47. doi: 10.55730/1300-0144.5482.
156. Wang Y, Wang L, Zhu X, Wang D, Li X. Choleretic Activity of Turmeric and its Active Ingredients. J Food Sci. 2016;81(7):H1800-6. doi: 10.1111/1750-3841.13348.
157. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012–. PMID: 31643176. Available from: https://pubmed.ncbi.nlm.nih.gov/31643176/. Accessed: Aug 26, 2023.
158. Biasi F, Leonarduzzi G, Oteiza PI, Poli G. Inflammatory Bowel Disease: Mechanisms, Redox Considerations, and Therapeutic Targets. Antioxid Redox Signal. 2013;19(14):1711-47. doi: 10.1089/ars.2012.4530.