REVIEW
Traditional Medicine Research 2024;9(10):60. https://doi.org/10.53388/TMR20240128002

Boswellic acids: a review on its pharmacological properties, molecular mechanism and bioavailability

Na Cui[1, 2, 3#], Ming-Jie Li[1#], Yi-Wen Wang[2, 3], Qian Meng[2], Ya-Jun Shi[3], Yi Ding[2*]

[1]Department of Pharmacy, 3201 Hospital, Hanzhong 723000, China. [2]Department of Pharmacy, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, China. [3]School of Pharmacy, Shaanxi University of Traditional Chinese medicine, Xianyang 712046, China.

[#]These authors contributed equally to this work and are co-first authors for this paper.
[*]**Correspondence to:** Yi Ding, Department of Pharmacy, Xijing Hospital, Fourth Military Medical University, No. 127, Changle West Road, Xincheng District, Xi'an 710032, China. E-mail: dingyi.007@163.com.

Author contributions
Na Cui and Mingjie Li conceived the study. Na Cui conducted literature review and wrote the manuscript. Yiwen Wang and Qian Meng drew figures and made tables in the manuscript. Yajun Shi and Yi Ding critically revised the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare no conflicts of interest.

Acknowledgments
This work was supported by the National Natural Science Foundation of China (82274313), Key R&D Program of Shaanxi Province (2023GHZD43).

Peer review information
Traditional Medicine Research thanks all anonymous reviewers for their contribution to the peer review of this paper.

Abbreviations
BA, boswellic acids; HPLC, high-performance liquid chromatography; MS, mass spectrometry; α-BA, α-boswellic acid; β-BA, β-boswellic acid; acetyl-α-BA, acetyl-α-boswellic acid; acetyl-β-BA, acetyl-β-boswellic acid; KBA, 11-keto-β-boswellic acid; AKBA, acetyl-11-keto-β-boswellic acid; NSAIDs, nonsteroidal anti-inflammatory drugs; 5-LOX, 5-lipoxygenase; IC_{50}, half maximal inhibitory concentration; COX-2, cyclooxygenase-2; NO, nitrogen monoxide; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; NF-κB, nuclear factor κB; HKBA, hexanoyloxy; HL-60, human promyelocytic leukemia; CNS, central nervous system; HO-1, heme oxygenase-1; ROS, reactive oxygen species; MIC, minimum inhibitory concentrations; APAP, acetaminophen; GR, glutathione; COVID-19, coronavirus disease 2019.

Citation
Cui N, Li MJ, Wang YW, Meng Q, Shi YJ, Ding Y. Boswellic acids: a review on its pharmacological properties, molecular mechanism and bioavailability. *Tradit Med Res.* 2024;9(10):60. doi: 10.53388/TMR20240128002.

Executive editor: Jing-Yi Wang.
Received: 28 January 2024; **Accepted:** 28 April 2024; **Available online:** 08 May 2024.

Abstract
Boswellic acids is a general term for a series of pentacyclic triterpenoid compounds that are isolated from the oleogin resin of the *Boswellia* genus and serve as the main active ingredient. It exhibits a wide range of biological activities, such as anti-inflammatory, anti-cancer, antibacterial, antiviral, hepatoprotective, neuroprotective, anti-diabetic, and anti-thrombotic properties. As a result, it has gained significant recognition among practitioners of traditional Chinese and Indian medicine. These biological effects may be associated with multiple molecular targets and signal transduction pathways. However, the poor pharmacokinetic properties of the substance lead to lower bioavailability, which affects its effectiveness. To address this issue, scientists have proposed a number of strategies, such as solid dispersions, phytosome® technologies, and novel drug delivery systems. This article aims to provide a comprehensive overview for boswellic acids on the phytochemistry, molecular mechanisms, potential therapeutic applications, and strategies to improve bioavailability.

Keywords: boswellic acids; molecular mechanism; pharmacological properties; bioavailability

Traditional Medicine Research 2024;9(10):60. https://doi.org/10.53388/TMR20240128002

Highlights

This review summarized the phytochemistry, molecular mechanisms, potential therapeutic applications, and strategies to enhance the bioavailability of boswellic acids.

Medical history of objective

Frankincense has been cultivated since ancient times in regions with special monsoon climates, such as the Arabian Peninsula, Somalia, Ethiopia, and India, and was sold to Europe and China via the Nabatat spice trade route 5,000 years ago. Frankincense resin has long been used in funerals and religious ceremonies, as well as in folk medicine to treat inflammatory diseases such as flatulence, constipation, central nervous system disorders, respiratory and gastrointestinal infections. In China, frankincense first appeared in "*Mingyi Bielu*" written by Tao Hongjing in the late Han Dynasty, which has effects on blood circulation, pain relief, swelling, and muscle gain. Frankincense was approved in Europe in the early 20th century to treat inflammation and was mentioned in the seventh supplement of the *European Pharmacopoeia* in 2006 C.E.

Background

The utilization of Chinese herbs and their extracts in the treatment of human diseases spans centuries, forming a cornerstone in the discovery and development of drugs [1–3]. Frankincense, a resin known since antiquity for its medicinal properties, has seen widespread usage in India, China, and African countries, and its popularity is rising in Western countries. It is the resin of *Boswellia carterii* Birdw. and *Boswellia bhaw-dajiana* Birdw., also known as Indian Frankincense. In China, it is called "Ru Xiang". The *Boswellia* genus comprises nearly 25 distinct species, some of the most important of which are *Boswellia serrata*, *Boswellia sacra*, and *Boswellia carterii* [4–6]. *B. serrata*, the most extensively researched species, is prevalent in India, the subcontinent, and Africa.

Boswellic acids (BA), isolated from the oleogin resin of the *Boswellia* genus, is a general term for a series of pentacyclic triterpenoid compounds, which serves as the main active ingredient. The presence of BA in almost all *Boswellian* species is a feature of this genus [7]. Recent research has highlighted its diverse pharmacological activities, including anti-inflammatory, antibacterial, anti-tumor, anti-oxidation, and anti-aging properties (Figure 1) [8]. Currently, BA has been used in a number of clinical studies, including trials for osteoarthritis, ulcerative colitis, rheumatoid arthritis, asthma, photoaging skin, and peritumoral cerebral edema [9–15]. Based on this background, BA and *Boswellia* extracts are considered a promising alternative for the treatment of chronic diseases. While BA has a variety of beneficial effects, pharmacokinetic studies have shown that its low bioavailability in humans and animals affects pharmacological effects [16]. Researchers have tried to solve the problem of poor bioavailability through a variety of strategies, and some progress has been made.

This review acknowledges the great potential of BA as therapeutic agents, deepens the understanding of their mechanism of action, and demonstrates strategies to improve their bioavailability. By highlighting these challenges, it is hoped that this review will stimulate further research in these areas. Improved characterization and modification of BA may lead to better therapeutic strategies, personalized treatments leveraging relevant signaling pathways, and ultimately the wider application of BA in medicine.

Phytochemistry

Currently, the identification of BA relies on various chromatographic techniques, such as thin-layer chromatography, high-performance liquid chromatography (HPLC), and supercritical fluid chromatography [17]. The most commonly used is still based on HPLC coupled with photodiode array detection [18]. In addition, the identification of BA is also indispensable to mass spectrometry (MS), which can further verify the structure of the compound. It is sometimes identified by means of ultraviolet spectrophotometry and nuclear magnetic resonance spectroscopy [19]. However, only analytical methods based on chromatography and mass spectrometry coupled together can accurately quantify and identify BA in *Boswellia serrata* extracts, whereas other methods based on HPLC or spectrophotometry alone cannot adequately and accurately quantify BA [20]. Accurate identification and quantification of BA is usually obtained by liquid chromatography electrospray ionization tandem mass spectrometry [21].

BA is essentially a series of pentacyclic triterpenoid compounds. So far, most of the BA components obtained from Boswellia can be divided into ursane, oleanane, or lupane families according to their parent nucleus structure. Among the representative compounds are α-boswellic acid (α-BA), β-boswellic acid (β-BA), acetyl-α-boswellic

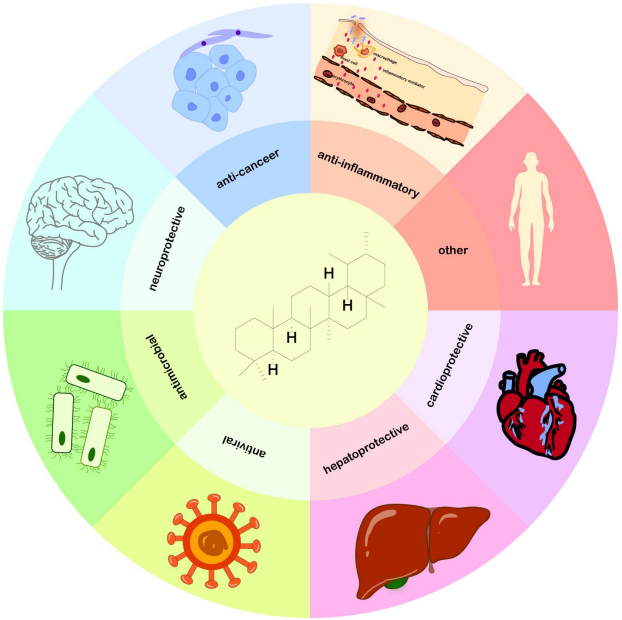

Figure 1 Biological effects of BA

acid (acetyl-α-BA), acetyl-β-boswellic acid (acetyl-β-BA), 11-keto-β-boswellic acid (KBA), and acetyl-11-keto-β-boswellic acid (AKBA) (Figure 2).

Quality control

Quality control is critical to the safety and effectiveness of drugs. Many fast, sensitive, and stable techniques have been applied to BA quality analysis. The main characteristics of the products obtained after the separation and purification of frankincense are BA, which account for more than 60% of the extract components [22]. The existing researches on the quality control of BA mainly focus on its component content determination and characteristic spectrum [23]. Most of the content determination studies only quantified AKBA, KBA, and other major components. At present, the relevant chromatographic detection technologies mainly include U/HPLC, gas chromatography, thin layer chromatography, supercritical fluid chromatography, and are often combined with other technologies, such as MS and ultraviolet spectrophotometry [24].

Pharmacology

Anti-inflammatory effects

Anti-inflammatory effects are one of the earliest discovered pharmacological properties of BA. The importance of this anti-inflammatory action cannot be underestimated, as chronic inflammation is known to contribute to the development of various diseases, such as heart disease, cancer, and autoimmune conditions. Although the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids is the conventional approach to managing inflammation, they are often associated with adverse effects. Therefore, BA from *Boswellia serrata* provides a promising alternative for developing new anti-inflammatory therapies that could potentially have less severe side effects.

BA showed dose-dependent efficacy in acute edema, adjuvant polyarthritis, chronic arthritis, and other models [25]. In a mouse model of colitis induced by sodium glucan sulfate, the semi-synthetic AKBA was found to significantly inhibit the recruitment of inflammatory cells, protect the colon mucosa, and reduce disease activity, rivaling the effects of dexamethasone. Additionally, semi-synthetic AKBA suppresses the recruitment of inflammatory cells by inhibiting P-selectin expression [26]. Norihiro Banno and colleagues isolated 15 triterpenic acids from frankincense, all of which demonstrated anti-inflammatory activity in a mouse inflammation model induced by 12-O-tetradecanoylphorbol-13-acetate [27]. BA, at a dose of 250 mg/kg, significantly inhibited both carrageenan-induced plantar edema and mycobacterium-induced developmental arthritis. When combined with glucosamine, its anti-arthritis effect was pronounced [28]. Boswellin Super® FJ, a standardized extract containing at least 30% AKBA and other β-BA, has been evaluated by Muhammed Majeed et al. for its activity and mechanism. Boswellin Super® treatment significantly reduced the arthritis index, foot volume, and joint inflammation in rats with collagen-induced arthritis and significantly inhibited inflammation such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), nitrogen monoxide (NO), and cyclooxygenase-2 (COX-2), compared to celecoxib [29]. In addition, BA has been shown to be effective in other inflammatory conditions. Acetyl-α-BA and acetyl-β-BA mixture reduced the release of inflammatory factors in lipopolysaccharide-stimulated RAW264.7 cells, suggesting an anti-inflammatory effect; it also significantly attenuated the infiltration of inflammatory cells in mice modeled for pancreatitis and significantly reduced the inflammatory factors in the serum through the modulation of MAPKs pathway [30]. These all suggest that acetyl-α-BA and acetyl-β-BA mixture has a certain therapeutic effect on acute pancreatitis.

Several studies have elucidated the anti-inflammatory molecular mechanisms of BA, pinpointing its action in inhibiting inflammatory factors and related pathways. Key molecular targets like 5-lipoxygenase (5-LOX) and microsomalprostaglandine-synthase-1 (mPGES-1) bind directly to BA, getting inhibited by these triterpenoid acids [31]. mPGES-1, an inducer of COX-2-derived prostaglandin H2 biosynthesis of pro-inflammatory prostaglandin E2, is considered a viable drug target to replace the COX enzymes blocked by NSAIDs, offering an effective and safe intervention in inflammatory diseases [32, 33]. Leukotrienes, significant mediators of inflammation and allergic reactions, are produced through the metabolism of arachidonic acid via the 5-LOX pathway [34]. AKBA has been identified as a natural inhibitor of the transcription factor nuclear factor κB (NF-κB), a crucial downstream mediator of cytokines during inflammation [35]. BA can down-regulate the phosphorylation of mitogen-activated protein kinase (MAPK) family phosphorylated proteins p38, extracellular regulated protein kinases (ERK)1/2, and JNK, thereby reducing serum inflammatory factors. It also diminishes the production of NO, TNF-α, IL-6, IL-10, and IL-1β stimulated by lipopolysaccharide in RAW264.7 cells, suggesting its anti-inflammatory effect [30].

Among the numerous anti-inflammatory several of BA, it is worth mentioning the inhibition of 5-LOX, an enzyme that catalyzes the conversion of arachidonic acid into leukotrienes. The specificity of BA's action on the 5-LOX enzyme distinguishes it from NSAIDs, which typically inhibit COX enzymes and can cause gastrointestinal side effects [36]. BA, therefore, provides a targeted approach to managing inflammation, and its lack of severe side effects often associated with NSAIDs is a notable advantage in pursuing BA-based therapies for long-term management of chronic inflammatory conditions.

In summary, the effectiveness of BA in the treatment of inflammatory diseases is attributed to its unique multimodal anti-inflammatory effects, which together address the complex pathology of these diseases.

Tumor inhibitory effects

BA has shown promise in the prevention and treatment of a broad spectrum of cancers, including breast, gastric, non-small cell lung, prostate, colon, head and neck, liver, lung, and pancreatic cancers. Researchers have even synthesized semi-synthetic derivatives of BA to enhance its anti-cancer efficacy [37]. AKBA has been found to inhibit the growth of colorectal cancer cells, potentially through the upregulation of specific miRNA pathways. Specifically, let-7 and miR-200, both presumed tumor suppressor miRNAs, play a crucial role in regulating cancer cell proliferation, migration, and invasion. AKBA significantly increases the expression of the let-7 and miR-200 families and modulates the expression of several downstream targets of these families, such as recombinant cyclin dependent kinase 6 (CDK6), vimentin, and E-cadherin [38]. Propionyl derivatives of 11-keto-β-boswellic acid (PKBA) exhibit greater anti-cancer potential than other BA, including AKBA. Butyryloxy and hexanoyloxy (HKBA) derivatives of KBA demonstrated lower half maximal inhibitory concentration (IC_{50}) values in human promyelocytic leukemia (HL-60) cells compared to the previously reported IC_{50} of 8.7 μg/mL for the PKBA derivative. The IC_{50} values for butyryloxy and HKBA were 7.7 and 4.5 μg/mL, respectively. Further studies on HKBA's activity revealed various markers, such as DNA fragmentation, apoptotic body formation, and Annexin-V binding, affirming its pro-apoptotic effect in HL-60 cells. HKBA treatment also caused a delay in the G2/M phase of cancer cells and a significant increase in the subG1 phase of the cell cycle [39].

BA mainly achieves its anti-tumor effect by inducing tumor cell death through various mechanisms (Table 1) [40–49]. This process is critical for the elimination of cancer cells and the prevention of tumor growth. BA can also inhibit tumor angiogenesis, a crucial factor in tumor growth, invasion, and metastasis. Vascular endothelial growth factor (VEGF) is widely expressed in most cancers and is a key component of tumor angiogenesis. BA inhibits downstream protein kinases of VEGFR2, including Src family kinases, focal adhesion kinases, extracellular signal-associated kinases, AKT, mammalian target of rapamycin, and ribosomal protein S6 kinases [50]. Additionally, BA produces anti-tumor activity by regulating autophagy and tumor cell proliferation [51].

Traditional Medicine Research 2024;9(10):60. https://doi.org/10.53388/TMR20240128002

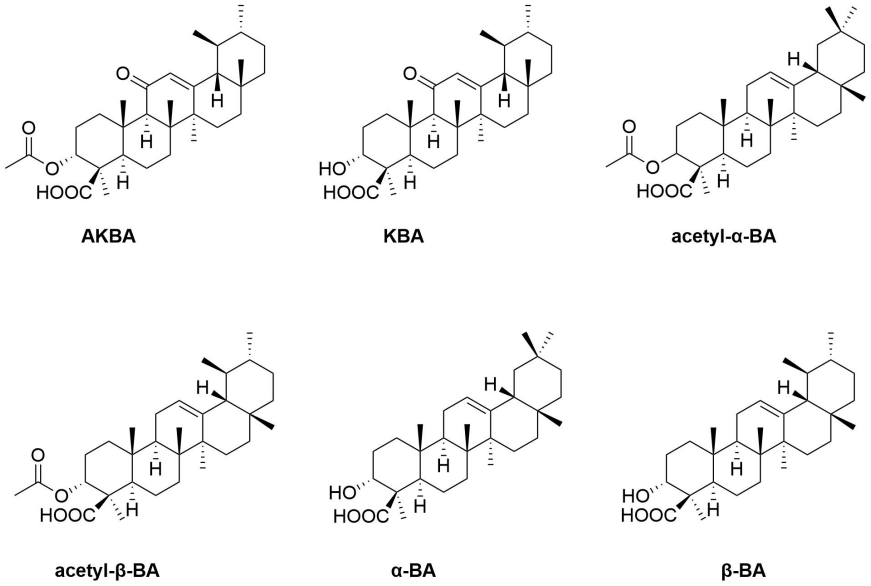

Figure 2 The six representative components of BA. KBA, 11-keto-β-boswellic acid; AKBA, acetyl-11-keto-β-boswellic acid; α-BA, α-boswellic acid; β-BA, β-boswellic acid; acetyl-α-BA, acetyl-α-boswellic acid; acetyl-β-BA, acetyl-β-boswellic acid.

Table 1 Inhibitory effect on tumor and mechanisms of BA

Disease/condition	Experimental setting	Mechanism	Reference
Gastric cancer	BGC823 and SGC7901, Human gastric cancer xenograft nude mouse model	Down-regulation of COX-2 expression through the PTEN/Akt signaling pathway.	[40]
Liver cancer	Hep G2 cells	Caspase-3, -8 and -9↑	[41]
Non-small cell lung cancer	NSCLC cell lines	P21↑, Bax↑, Bcl-2↓	[42]
Prostate cancer	LNCaP and PC-3 human prostate cancer cells and docetaxel-resistant PC3/Doc cells, docetaxel-resistant PCa homograft mice model	Caspase-3 and -9↓, increased the levels of CAAT/enhancer binding protein homologous protein and activated a recombinant death receptor 5 (DR5) promoter reporter, blocking Akt, and transcriptional signaling and activator 3 (STAT-3) signaling.	[43, 44]
Breast cancer	MDA-MB-231 cells, MCF-7 cells, and MDA-MB-231 cell lines, the breast precancerous rat model	P53↑, Bcl-2↓, GLUT1 targeting-induced glycolysis suppression and activated the AMPK pathway and inhibited the mTOR pathway.	[45, 46]
Colorectal cancer	HCT-116 p53−/− cells, Orthotopic human colorectal cancer mouse model	Cyclin D1 and E, CDK 2 and 4 and phosphorylated Rb↓, p21↑, NF-κB, cyclooxygenase-2, Bcl-2, Bcl-xL, inhibitor of apoptosis, intercellular adhesion molecule 1, and matrix metalloproteinase-9↓	[47]
Leukemia	HL-60 cells	Inhibition of topoisomerases I and II	[48]
Melanoma	Against fibroblast cells	P53 and Bax/Bcl2↑, Bcl2↓	[49]

COX-2, cyclooxygenase-2; HL-60, human promyelocytic leukemia; NF-κB, nuclear factor κB.

Based on these promising cellular and molecular effects, BA is being studied extensively to determine their therapeutic potential in cancer treatment. They may be incorporated into novel therapeutic strategies, either as standalone agents or in combination with other anticancer drugs to enhance efficacy. As research progresses, BA could become an important part of the oncologist's arsenal, providing new hope for patients afflicted by cancer. As research progresses, BA could become an important tool for oncologists, offering hope to cancer patients.

Neuroprotective effects

BA has emerged as a notable player in the realm of neuroprotection. Studies have consistently shown that BA exerts beneficial effects across a range of central nervous system (CNS) disorders, encompassing neurodegenerative diseases, stroke, and traumatic brain injury, to name a few. The neuroprotective properties of these molecules are mainly attributed to their powerful anti-inflammatory and antioxidant capabilities. BA has shown therapeutic potential for CNS diseases such as neurotoxicity, neurodegenerative diseases, and brain injury (Table 2) [52–57]. Inflammation is a known pathogenic mechanism in numerous CNS disorders, contributing to disease progression and ultimately leading to neuronal injury or death. BA has been found to modulate inflammatory responses within the brain and spinal cord. BA can lead to a reduction in the expression of pro-inflammatory cytokines and mediators such as TNF-α, IL-1β, IL-6, and NF-κB [58]. In addition to their anti-inflammatory properties, BA may also contribute to the regulation of apoptosis, further bolstering their neuroprotective effects [59]. They have been reported to enhance the expression of neurotrophic factors, which support neuron survival and regeneration [60, 61]. This multifaceted approach underscores the therapeutic potential of BA in mitigating the impact of CNS disorders.

Table 2 Neuroprotective effects and mechanisms of BA

Compounds	Disease/condition	Experimental setting	Mechanism	Reference
AKBA	Ischemic stroke	Oxygen and glucose deprivation model and rat middle cerebral artery occlusion model	Nuclear factor erythroid-2-related factor 2 (Nrf-2) and heme oxygenase-1 (HO-1)↑, inflammatory proteins↓, blocked the degradation of Zonula occluden-1 (ZO-1) and occludin after oxygen and glucose deprivation.	[52, 53]
α-BA	Alzheimer's disease	Streptozotocin was utilized to induce Alzheimer's disease condition in astrocytes.	Reelin↑, hyperphosphorylated Tau (Ser404)↓, and reactive oxygen species (ROS)↓	[54]
AKBA	Spinal cord injury	Surgically induced animal models	Involved in the Nrf2-ROS-NLRP3 pathway, caspase-1↓, GSDMD↓, IL-18↓, IL-1β↓.	[55]
AKBA	Amyotrophic lateral sclerosis	MeHg-induced experimental amyotrophic lateral sclerosis model	Nrf-2 and HO-1↑	[56]
β-BA	Huntington's disease	3-nitropropionic acid induced Huntington's disease in rats	Reduces cytokine production while restoring mitochondrial electron transport chain complex enzymes, neurotransmitter imbalances and antioxidant potential.	[57]

AKBA, acetyl-11-keto-β-boswellic acid; α-BA, α-boswellic acid; β-BA, β-boswellic acid.

As our understanding deepens, this may open new avenues for strategies to utilize the neuroprotective properties of BA in the treatment of CNS disorders and hold promise for improving the care of patients with CNS disorders.

Antimicrobial effects

AKBA is the most important active ingredient in BA, with an minimum inhibitory concentrations (MIC) range of 2–8 μg/mL against all Gram-positive pathogens. Its killing effect on *Staphylococcus aureus* ATCC 29213 is up to 8 times the MIC, and it shows a 4.8-h post-antibiotic effect at 2 times the MIC. Furthermore, AKBA effectively inhibits the formation of biofilms produced by both *Staphylococcus aureus* and *Staphylococcus epidermidis*. It also reduces the preformation of biofilms by these bacteria. The increased uptake of propidium iodide in AKBA-treated *Staphylococcus aureus* cells suggests that AKBA modifies the structure of the cell membrane, resulting in the breakdown of the microbial membrane permeability barrier. Under treatment with 64 μg/mL AKBA, the leakage of cytoplasmic components (260 nm and 280 nm absorbent substances) of *Staphylococcus aureus* cells was significantly higher than the background level within 2 h. These observations suggest that AKBA's antimicrobial activity stems from its ability to disrupt the permeable barrier of microbial membrane structures [62]. Muralidhar et al. synthesized AKBA silver nanoparticles by phytochemistry and evaluated them in a mouse model of mastitis induced by *Staphylococcus aureus* [63]. The results showed that the nanoparticle significantly reduced breast bacterial load, serum C-reactive protein (CRP), superoxide dismutase (SOD) and catalase (CAT) activity, and neutrophil infiltration. It has better antibacterial, anti-inflammatory, and antioxidant properties than cefepime [64].

Hepatoprotective effects

Liver disease is a global problem, and the potential of ingredients derived from medicinal plants to prevent and treat hepatotoxic injuries has become a major research focus [65, 66]. Studies have shown that BA exerts hepatoprotective effects by inhibiting oxidative stress, inflammation, and apoptosis indicators in response to different models of hepatotoxicity. BA has a protective effect against acetaminophen (APAP)-induced hepatotoxicity in Balb/cA mice. BA preserves GR (glutathione) in the liver by maintaining glutathione content and reducing the formation of ROS and oxidized glutathione. The activity and expression of reductase and HO-1 are decreased, and the activity and expression of hepatocyte cytochrome P450 2E1 are reduced to relieve APAP-induced oxidative stress. Moreover, the release of inflammatory cytokines and chemokines induced by APAP is decreased, and the expression of NF-κB p65 and p-JNK is inhibited [67]. Zaitone et al. evaluated the protective effect of BA in a diet-induced rat model of non-alcoholic fatty liver disease and compared it with the standard insulin sensitizer pioglitazone [68]. The results showed that rats treated with BA (125 or 250 mg/kg) or pioglitazone improved insulin sensitivity and decreased liver index, liver enzyme activity, serum inflammatory factor levels, as well as liver iNOS expression and 4-hydroxy-2-nonenal (HNE) formation. In addition, the expression of certain proteins, such as heat-associated mitochondrial disconnect protein-1 and carnitine palmitoyltransferase-1, can be increased at the cellular level when the BA dosage reaches 250 mg/kg. Elgazar et al. prepared 23 novel hybrids based on AKBA using a variety of biocompatible linkers and evaluated the hepatoprotective potential of these hybrids for APAP toxicity [69]. Both hybrids effectively restored elevated cytokine levels caused by APAP to normal levels. Additionally, they normalized levels of superoxide dismutase and glutathione while significantly reducing malondialdehyde levels.

Other effects

BA showed some hypoglycemic effects in diabetes models, either administered alone or as a supplement to known hypoglycemic agents. β-BA and β-KBA significantly reduced the blood glucose level of fasting streptozotocin-induced diabetic rats, significantly lowered blood lipids, and lowered various biochemical indexes such as serum glutamic pyruvic (SGPT), serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase (ALP), and serum creatinine in diabetic rats. It indicated that β-BA and β-KBA have strong anti-diabetic potential [70]. In diabetic rats, the enhancement of the hypoglycemic effect of glibenclamide in combination with BA or andrographolide was significantly greater than that of the drug alone and in combination with the control group, suggesting that glibenclamide in combination with BA or andrographolide enhances the hypoglycemic ability of diabetic rats [71]. The hypolipidemic effect of BA has been demonstrated in several studies. The aqueous extract of *Boswellia serrata* showed strong hypocholesterolemic effects and increased serum high-density lipoprotein levels in animal studies. It also inhibited NO production, showing hepatoprotective and renoprotective effects [72]. The inhibitory effect of AKBA on NF-κB activity in atherosclerosis makes it a possible alternative to conventional drugs for the treatment of chronic inflammatory diseases

such as atherosclerosis [35]. AKBA has a dose-dependent effect on renal interstitial fibrosis both in vivo and in vitro, and its mechanism may be related to the inhibition of Klotho/TGF-β/Smad signaling pathway. In experimental renal fibrosis model induced by unilateral ureteral obstruction in AKBA mice, the expression of TGF-β1, α-SMA, type I collagen, and type IV collagen in damaged tissues was reduced significantly to alleviate renal damage caused by unilateral ureteral obstruction and improve renal fibrosis. Using hypoxia-induced HK-2 cells to simulate the pathological process of renal fibrosis in vitro, AKBA showed significant cytoprotective and anti-fibrotic properties by increasing cell viability, decreasing the release of lactate dehydrogenase (LDH) and inhibiting the expression of fibrotic factors [73]. Furthermore, researches have shown that KBA exerts a dose-dependent cardioprotective effect on cardiac ischemia-reperfusion injury, and the mechanism may be related to enhancing antioxidant capacity and preventing inflammatory cascades [74].

Clinical trials and human

Studies have demonstrated that BA has robust pharmacological activity in preclinical studies and has validated its therapeutic potential in various chronic diseases through clinical trials.

Coronavirus disease 2019 (COVID-19)

The antiviral therapy of traditional Chinese medicine has the advantages of broad-spectrum application, low toxicity and side effects, and comprehensive integrated regulation. Therefore, research on the antiviral effects of traditional Chinese medicines and their active ingredients has received increasing attention. Recent studies have suggested a potential therapeutic role for BA in treating COVID-19. Gomaa et al. conducted a randomized, double-blind, placebo-controlled, and single-center study (identifier NCT04487964) to assess the efficacy of GR + BA versus placebo in hospitalized patients with moderate SARS-CoV-2 or COVID-19 variant infection. Patients received 60 mg GR capsules and 200 mg BA orally twice daily for 14 days, alongside standard COVID-19 treatment protocols. Primary outcome assessments on day 14 revealed significantly lower mortality and shorter recovery times in the GR + BA group, compared to placebo, suggesting that this combination might be an effective, safe, and low-cost option for treating mild to moderate COVID-19 infections [75].

Osteoarthritis

In a randomized, double-blind, placebo-controlled clinical trial, Aflapin® (aprsflex®), a bioavailability-enhanced *Boswellia serrata* extract standardized to 20% AKBA, demonstrated efficacy in alleviating symptoms of knee osteoarthritis without significant adverse effects. Participants experienced significant improvements in pain, physical function, and inflammation markers, indicating Aflapin® as a promising therapeutic agent for osteoarthritis [76].

Alzheimer's disease

A placebo-controlled clinical trial involving patients with mild to moderate Alzheimer's disease showed significant improvements in cognitive function and neuropsychiatric symptoms in patients treated with Boswellia. This study, utilizing a daily dose of 1,200 mg of a concentrated BA (K-Vie™), also reported lower levels of key pro-inflammatory cytokines and a higher amyloid-β42/amyloid-β40 ratio in the treatment group, with no serious adverse events noted [77].

Breast cancer

A Phase I clinical trial investigating the bioactivity and safety of *Boswellia serrata* in breast cancer patients showed a significant reduction in tumor cell proliferation in the treatment group compared to the control group. The trial, which involved administering *Boswellia serrata* (2,400 mg/day PO) pre-surgery, confirmed its potential as a safe and effective treatment option for breast cancer [78].

Burn

A randomized, double-blind clinical trial comparing a *Boswellia*-based herbal formula with 1% silver sulfadiazine cream in treating second-degree burns demonstrated comparable efficacy in wound healing. This suggests that *Boswellia* formulations could serve as an alternative to standard burn treatments [79].

Pharmacokinetics and bioavailability

Pharmacokinetics

The absorption of BA in the human body is a complex process, influenced by various physiological and molecular factors. One of the key elements affecting the absorption of BA is their solubility, which is often related to the chemical nature of the substance. Solubility can be affected by pH within the gastrointestinal tract, which varies substantially from the stomach to the intestines. Substances that are soluble in aqueous environments have a higher likelihood of being absorbed because they can dissolve in the gastrointestinal fluids, thereby facilitating their transport across the intestinal lining.

Permeability is another crucial factor determining BA absorption. It refers to the ability of a compound to cross biological membranes, such as the epithelial cells that line the gastrointestinal tract. The permeability of a compound is generally assessed using models like the Caco-2 cell culture system, which simulates the human intestinal barrier.

Although lipophilic compounds are thought to diffuse more rapidly across the intestinal epithelial cell membrane, which is a major barrier to oral absorption, current research suggests that lipophilic pentacyclic triterpenoids such as KBA and AKBA may also reduce the ability to cross the Caco-2 monolayer. Kruger's results show that the apparent permeability coefficient of KBA is 1.69×10^{-6} cm/s, which is moderate, while only a small fraction of AKBA is able to pass through Caco-2 cells with a penetration rate of no more than 0.05%, which corresponds to the lower limit of the quantification of the analytical method used in the experiment [80]. This may be the reason for the low bioavailability of BA.

After absorption, BA was distributed most abundantly in the liver and kidney only, in addition to the plasma [81]. Two hours after administration, the compounds and their metabolites were analyzed by liquid chromatography tandem mass spectrometry. It was found that KBA and AKBA were present in plasma, liver, and brain, and there were partially hydroxylated metabolites of KBA in plasma and liver, while no hydroxylated metabolites of AKBA were detected in plasma, liver, and brain. In addition, similar metabolic profiles were found in vitro. Overall, KBA was metabolized in vitro and in vivo to several hydroxylated compounds that were present in the rat liver but not in the brain. AKBA was metabolized in small amounts in vivo and in vitro, and conjugated derivatives of the compound and metabolite were not detected in vitro or in vivo. Like KBA previously observed in the same model, β-BA underwent extensive phase I metabolism in both human and rat liver microsomes; α-BA was extensively metabolized in human liver microsomes and was not metabolized in rat liver microsomes; and acetylated Acetyl-α-BA and Acetyl-β-BA were as metabolically stable as AKBA [82]. In addition, the non-acetylated and more hydrophilic BA had significant phase I metabolism and is expected to be excreted in the urine [83].

Innovative strategies to enhance bioavailability

Pharmacokinetic studies of BA have revealed poor bioavailability, especially concerning the major active components KBA and AKBA [84]. Several studies have shown that despite the oral administration of large doses of latex acid derivatives, little or no detection of these active derivatives has been observed in human biological blood or fluids. The current scientific hypothesis is that malabsorption and high metabolism of BA may be responsible for the low bioavailability [85]. In contrast, low water solubility and hydrophobicity are the main causes of malabsorption after oral administration.

In the pharmaceutical industry, the term "bioavailability" refers to

the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. Poor bioavailability is a significant hurdle that can limit the efficacy of many drugs. As such, researchers are exploring innovative strategies to enhance bioavailability and thereby increase the therapeutic benefit of drugs.

One promising strategy is the development of novel drug formulations. This can involve the use of new excipients, substances that are included in the drug product to aid in the processing of the active ingredient. Excipients can stabilize the drug, enhance its absorption, or control its release over time. For instance, solid dispersion techniques, where the drug is dispersed in a solid matrix, can be used to increase the solubility and, consequently, the bioavailability of poorly soluble drugs. In addition, Phytosome® technology has been successfully applied to herbal extracts, such as ginkgo, milk thistle, and green tea, as well as phytochemicals, such as curcumin and silymarin, with remarkable results in both animal and human pharmacokinetic studies. Tambe et al. prepared solid dispersions using cyclodextrin and poloxamer, respectively, to enhance intestinal absorption of AKBA in the total BA fraction [86]. Intestinal absorption studies have shown that HP-β-CD complex and PXM 407 SD have the highest absorption of AKBA compared to other components. Additionally, Hüsch et al. utilized Phytosome® technology to create Casperome™. It is a soy lecithin formulation containing a standardized lactic acid extract. Oral administration of Casperom™ with the equivalent body weight and equimolar significantly increased plasma levels (up to 7 times the KBA, 3 times the β-BA quantified by AUClast in the region under the plasma concentration time curve) compared to undeveloped extracts. This is accompanied by significantly higher tissue levels. Of particular relevance, Casperome™ administration resulted in significant increases in brain KBA and AKBA concentrations (35-fold) and β-BA (3-fold). Additionally, these findings highlight the importance of Casperome™ in enhancing brain KBA and AKBA concentrations, as well as β-BA levels. Notably, BA levels were as high as 17-fold in worse vascularized organs (the eye) [81].

Novel drug delivery systems are another area of intense study and are important ways to improve the bioavailability and pharmacokinetic properties of BA. For example, liposomes, nanostructured lipid carriers, and polymeric nanoparticles have been used to improve the bioavailability and therapeutic efficacy of BA (Table 3) [87–94].

Techniques such as the use of self-emulsifying drug delivery systems are also gaining attention. Self-emulsifying drug delivery systems can form emulsions in the gastrointestinal tract, which can enhance the solubility and absorption of lipophilic drugs. Additionally, mucoadhesive particles can be employed to prolong the residence time of a drug at the absorption site, thus increasing bioavailability. A study was conducted to increase the systemic concentration of BA by using a self-nanoemulsifying system. In lipolysis studies, the aqueous solubility and bioaccessibility of KBA and AKBA were increased by 2.7-fold and 2.3-fold, respectively. From in vivo pharmacokinetic studies, self-nanoemulsifying system significantly increased the oral bioavailability of KBA and AKBA by 2.2-fold and 2.0-fold, respectively, over the bulk oil suspension [95].

Moreover, chemical modifications of drugs, such as prodrugs, where an inactive compound is metabolized into an active drug in the body, can help overcome barriers to drug absorption. These modifications can mask undesirable properties of the parent drug molecule, making it more amenable to absorption.

Table 3 Novel drug delivery systems for BA

Nanoformulations	Materials	Disease/condition	Advantage	Reference
Nano metal-organic frameworks	The pH sensitive zeolitic imidazolate framework-8 nanocomposite	Breast cancer	Higher efficacy, better biocompatibility, enhanced adsorption/desorption kinetics, and tiny size	[87]
Ultradeformable vesicular carriers (transferosomes)	Polymers such as starch and HPMC K4M	Transdermal drug delivery	Enhance permeability and bioavailability along with improving circulation time in blood and drug release	[88]
Spanlastic nanovesicles	Span 60 and Tween 80	Topical delivery	Optimized the topical delivery and the permeability of AKBA	[89]
Polymeric nanomicelles	N-isopropylacrylamide, vinylpyrrolidone and acrylic acid	Topical delivery	Three-fold increase in skin permeability and significant enhancement of pharmacological activity	[90]
Guggul gum-chitosan nanoparticles	Guggul gum and chitosan	Carrageenan-induced hind paw inflammation in rats	11.38-fold increase in bioavailability, good stability, specific drug delivery	[91]
Poly(lactic-co-glycolic acid) nanoparticle	Poly(lactic-co-glycolic acid)	Carrageenan-induced rat paw oedema	Improved bioavailability and enhanced anti-inflammatory activity in vivo	[92]
Dendrosome nanoparticle	Dendrosome	Memory performance	Improved its uptake by the cells and enhanced the impact of β-BA on the memory performance	[93]
Silver nanoparticles	Silver nitrate solution	Carrageenan-induced rat paw edema	Safety, less toxic and therapeutically active	[94]

AKBA, acetyl-11-keto-β-boswellic acid; β-BA, β-boswellic acid.

Toxicity

Multiple studies have confirmed that BA has a broad-spectrum safety profile, both in preclinical models and in human studies. Bacterial reverse mutation assay, bone marrow chromosome aberration assay, and bone marrow micronucleus assay showed that B. serrata extracts are non-mutagenic [96]. In numerous in vivo animal experiments, BA was considered generally safe at experimental doses (100 mg/kg) and did not result in weight loss, skin irritation, or changes in biochemical or histopathological parameters [97, 98].

Conclusions

BA is a class of pentacyclic triterpenes, which is the active component of frankincense. Because of its strong pharmacological activity, it is a hot topic in the field of synthesis and medicinal chemistry. Natural BA and its synthetic derivatives have been used in the treatment of various diseases, especially in various cancers and inflammatory diseases. However, its poor solubility affects its bioavailability and limits its development. Encouragingly, recent advances in drug delivery systems, particularly nanoparticles, have shown promising results in overcoming these challenges. The continuous exploration and optimization of BA administration methods is expected to further unlock its potential as a multifunctional therapeutic agent.

References

1. Aafi E, Reza M, Mirabzadeh M. Jujube (Ziziphus jujuba Mill. (Rhamnaceae)): a review on its pharmacological properties and phytochemistry. *Tradit Med Res.* 2022;7(4):38. Available at: http://doi.org/10.53388/tmr20220905001
2. Zhou YY, Xiang RX, Qin GZ, et al. Xanthones from Securidaca inappendiculata Hassk. attenuate collagen-induced arthritis in rats by inhibiting the nicotinamide phosphoribosytransferase/glycolysis pathway and macrophage polarization. *Int Immunopharmacol.* 2022;111:109137. Available at: http://doi.org/10.1016/j.intimp.2022.109137
3. Sun SP, Li SL, Du YY, et al. Anti-inflammatory effects of the root, stem and leaf extracts of Chloranthus serratus on adjuvant-induced arthritis in rats. *Pharm Biol.* 2020;58(1):528–537. Available at: http://doi.org/10.1080/13880209.2020.1767159
4. Woolley CL, Suhail MM, Smith BL, et al. Chemical differentiation of Boswellia sacra and Boswellia carterii essential oils by gas chromatography and chiral gas chromatography–mass spectrometry. *J Chromatogr A.* 2012;1261:158–163. Available at: http://doi.org/10.1016/j.chroma.2012.06.073
5. Blain EJ, Ali AY, Duance VC. Boswellia frereana (frankincense) suppresses cytokine-induced matrix metalloproteinase expression and production of pro-inflammatory molecules in articular cartilage. *Phytother Res.* 2010;24(6):905–912. Available at: http://doi.org/10.1002/ptr.3055
6. De Rapper S, Van Vuuren SF, Kamatou GPP, et al. The additive and synergistic antimicrobial effects of select frankincense and myrrh oils - a combination from the pharaonic pharmacopoeia. *Lett Appl Microbiol.* 2012;54(4):352–358. Available at: http://doi.org/10.1111/j.1472-765X.2012.03216.x
7. Shah BA, Qazi GN, Taneja SC. Boswellic acids: a group of medicinally important compounds. *Nat Prod Rep.* 2009;26(1):72–89. Available at: http://doi.org/10.1039/B809437N
8. Ragab EA, Abd El-Wahab MF, Doghish AS, et al. The journey of boswellic acids from synthesis to pharmacological activities. *Naunyn Schmiedebergs Arch Pharmacol.* 2023;397(3):1477–1504. Available at: http://doi.org/10.1007/s00210-023-02725-w
9. Sengupta K, Krishnaraju AV, Vishal AA, et al. Comparative efficacy and tolerability of 5-Loxin and AflapinAgainst osteoarthritis of the knee: a double blind, randomized, placebo controlled clinical study. *Int J Med Sci.* 2010:7(6)366–377. Available at: http://doi.org/10.7150/ijms.7.366
10. Notarnicola A, Tafuri S, Fusaro L, et al. The "MESACA" study: Methylsulfonylmethane and boswellic acids in the treatment of gonarthrosis. *Adv Ther.* 2011;28(10):894–906. Available at: http://doi.org/10.1007/s12325-011-0068-3
11. Sengupta K, Alluri KV, Satish A, et al. 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. Available at: http://doi.org/10.1186/ar2461
12. Sander O, Herborn G, Rau R. Is H15 (resin extract of Boswellia serrata, "incense") a useful supplement to established drug therapy of chronic polyarthritis? Results of a double-blind pilot study. *Z Rheumatol.* 1998;57(1):11–16. Available at: http://doi.org/10.1007/s003930050051
13. Gupta I, Gupta V, Parihar A, 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;3(11):511–514. Available at: https://pubmed.ncbi.nlm.nih.gov/9810030/
14. Pedretti A, Capezzera R, Zane C, et al. 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):555–560. Available at: http://doi.org/10.1055/s-0029-1240581
15. Kirste S, Treier M, Wehrle SJ, et al. Boswellia serrata acts on cerebral edema in patients irradiated for brain tumors. *Cancer.* 2011;117(16):3788–3795. Available at: http://doi.org/10.1002/cncr.25945
16. Du ZY, Liu ZL, Ning ZC, et al. Prospects of boswellic acids as potential pharmaceutics. *Planta Med.* 2015;81(4):259–271. Available at: http://doi.org/10.1055/s-0034-1396313
17. 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. Available at: http://doi.org/10.1016/j.jpba.2021.114106
18. Büchele B, Zugmaier W, Simmet T. Analysis of pentacyclic triterpenic acids from frankincense gum resins and related phytopharmaceuticals by high-performance liquid chromatography. Identification of lupeolic acid, a novel pentacyclic triterpene. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2003;791(1–2):21–30. Available at: http://doi.org/10.1016/s1570-0232(03)00160-0
19. Paul M, Brüning G, Bergmann J, et al. A thin-layer chromatography method for the identification of three different olibanum resins (Boswellia serrata, Boswellia papyrifera and Boswellia carterii, respectively, Boswellia sacra). *Phytochem Anal.* 2012;23(2):184–189. Available at: http://doi.org/10.1002/pca.1341
20. Katragunta K, Siva B, Kondepudi N, et al. Estimation of boswellic acids in herbal formulations containing Boswellia serrata extract and comprehensive characterization of secondary metabolites using UPLC-Q-Tof-MSe. *J Pharm Anal.* 2019;9(6):414–422. Available at: http://doi.org/10.1016/j.jpha.2019.09.007
21. Mannino G, Occhipinti A, Maffei ME. Quantitative Determination of 3-O-Acetyl-11-Keto-β Boswellic Acid (AKBA) and Other Boswellic Acids in Boswellia sacra Flueck (syn. B. carteri Birdw) and Boswellia serrata Roxb. *Molecules.* 2016;21(10):1329. Available at:

http://doi.org/10.3390/molecules21101329
22. Meins J, Artaria C, Riva A, et al. Survey on the quality of the top-selling European and American botanical dietary supplements containing boswellic acids. *Planta Med.* 2016;82(6):573–579. Available at: http://doi.org/10.1055/s-0042-103497
23. Huang K, Chen YR, Liang KY, et al. Review of the chemical composition, pharmacological effects, pharmacokinetics, and quality control of Boswellia carterii. *Evid Based Complement Alternat Med.* 2022;2022:6627104. Available at: http://doi.org/10.1155/2022/6627104
24. Kosolapov D, Jáč P, Riasová P, et al. Advances and challenges in the analysis of boswellic acids by separation methods. *Crit Rev Anal Chem.* 2024;1–27. Available at: http://doi.org/10.1080/10408347.2024.2312502
25. Hussain H, Al-Harrasi A, Csuk R, et al. Therapeutic potential of boswellic acids: a patent review (1990-2015). *Expert Opin Ther Pat.* 2017;27(1):81–90. Available at: http://doi.org/10.1080/13543776.2017.1235156
26. Anthoni C, Laukoetter MG, Rijcken E, et al. Mechanisms underlying the anti-inflammatory actions of boswellic acid derivatives in experimental colitis. *Am J Physiol Gastrointest Liver Physiol.* 2006;290(6):G1131–G1137. Available at: http://doi.org/10.1152/ajpgi.00562.2005
27. Banno N, Akihisa T, Yasukawa K, et al. Anti-inflammatory activities of the triterpene acids from the resin of Boswellia carteri. *J Ethnopharmacol.* 2006;107(2):249–253. Available at: http://doi.org/10.1016/j.jep.2006.03.006
28. Singh S, Khajuria A, Taneja SC, et al. Boswellic acids and glucosamine show synergistic effect in preclinical anti-inflammatory study in rats. *Bioorg Med Chem Lett.* 2007;17(13):3706–3711. Available at: http://doi.org/10.1016/j.bmcl.2007.04.034
29. Majeed M, Nagabhushanam K, Lawrence L, et al. Boswellia serrata extract containing 30% 3-Acetyl-11-Keto-boswellic acid attenuates inflammatory mediators and preserves extracellular matrix in collagen-induced arthritis. *Front Physiol.* 2021;12:735247. Available at: http://doi.org/10.3389/fphys.2021.735247
30. Zhang PY, Yu B, Men WJ, et al. Acetyl-α-boswellic acid and Acetyl-β-boswellic acid protects against caerulein-induced pancreatitis via down-regulating MAPKs in mice. *Int Immunopharmacol.* 2020;86:106682. Available at: http://doi.org/10.1016/j.intimp.2020.106682
31. Börner F, Werner M, Ertelt J, et al. Analysis of boswellic acid contents and related pharmacological activities of frankincense-based remedies that modulate inflammation. *Pharmaceuticals* (*Basel*). 2021;14(7):660. Available at: http://doi.org/10.3390/ph14070660
32. Bergqvist F, Morgenstern R, Jakobsson PJ. A review on mPGES-1 inhibitors: From preclinical studies to clinical applications. *Prostaglandins Other Lipid Mediat.* 2020;147:106383. Available at: http://doi.org/10.1016/j.prostaglandins.2019.106383
33. Smith WL, Urade Y, Jakobsson PJ. Enzymes of the cyclooxygenase pathways of prostanoid biosynthesis. *Chem Rev.* 2011;111(10):5821–5865. Available at: http://doi.org/10.1021/cr2002992
34. Kretzer C, Jordan PM, Bilancia R, et al. Shifting the biosynthesis of leukotrienes toward specialized pro-resolving mediators by the 5-lipoxygenase-activating protein (FLAP) antagonist BRP-201. *J Inflamm Res.* 2022;15:911–925. Available at: http://doi.org/10.2147/JIR.S345510
35. Cuaz-Pérolin C, Billiet L, Baugé E, et al. Antiinflammatory and antiatherogenic effects of the NF-κB inhibitor acetyl-11-keto-β-boswellic acid in LPS-Challenged ApoE$^{-/-}$ mice. *Arterioscler Thromb Vasc Biol.* 2008;28(2):272–277. Available at: http://doi.org/10.1161/ATVBAHA.107.155606
36. 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):349–369. Available at: http://doi.org/10.2165/11586800-000000000-00000
37. Shen Y, Takahashi M, Byun HM, et al. Boswellic acid induces epigenetic alterations by modulating DNA methylation in colorectal cancer cells. *Cancer Biol Ther.* 2012;13(7):542–552. Available at: http://doi.org/10.4161/cbt.19604
38. Takahashi M, Sung B, Shen Y, et al. Boswellic acid exerts antitumor effects in colorectal cancer cells by modulating expression of the let-7 and miR-200 microRNA family. *Carcinogenesis.* 2012;33(12):2441–2449. Available at: http://doi.org/10.1093/carcin/bgs286
39. Chashoo G, Singh SK, Mondhe DM, et al. Potentiation of the antitumor effect of 11-keto-β-boswellic acid by its 3-α-hexanoyloxy derivative. *Eur J Pharmacol.* 2011;668(3):390–400. Available at: http://doi.org/10.1016/j.ejphar.2011.07.024
40. Sun MX, He XP, Huang PY, 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):5822–5835. Available at: http://doi.org/10.3748/wjg.v26.i38.5822
41. Liu JJ, Nilsson A, Oredsson S, et al. Keto-and acetyl-keto-boswellic acids inhibit proliferation and induce apoptosis in Hep G2 cells via a caspase-8 dependent pathway. *Int J Mol Med.* 2002:10(4):501–505. Available at: http://doi.org/10.3892/ijmm.10.4.501
42. Lv MH, Zhuang XB, Zhang Q, et al. Acetyl-11-keto-β-boswellic acid enhances the cisplatin sensitivity of non-small cell lung cancer cells through cell cycle arrest, apoptosis induction, and autophagy suppression via p21-dependent signaling pathway. *Cell Biol Toxicol.* 2021;37(2):209–228. Available at: http://doi.org/10.1007/s10565-020-09541-5
43. Lu M, Xia LJ, Hua HM, et al. Acetyl-keto-β-boswellic acid induces apoptosis through a death receptor 5–mediated pathway in prostate cancer cells. *Cancer Res.* 2008;68(4):1180–1186. Available at: http://doi.org/10.1158/0008-5472.CAN-07-2978
44. Liu YQ, Wang SK, Xu QQ, 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):689–698. Available at: http://doi.org/10.1038/s41401-018-0157-9
45. Jamshidi-Adegani F, Ghaemi S, Al-Hashmi S, et al. Comparative study of the cytotoxicity, apoptotic, and epigenetic effects of Boswellic acid derivatives on breast cancer. *Sci Rep.* 2022;12(1):19979. Available at: http://doi.org/10.1038/s41598-022-24229-y
46. Bie FJ, Zhang GJ, Yan XX, et al. β-boswellic acid suppresses breast precancerous lesions via GLUT1 targeting-mediated glycolysis inhibition and AMPK pathway activation. *Front Oncol.* 2022;12:896904. Available at: http://doi.org/10.3389/fonc.2022.896904
47. Yadav VR, Prasad S, Sung B, 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.* 2011;130(9):2176–2184. Available at: http://doi.org/10.1002/ijc.26251
48. Chashoo G, Singh SK, Sharma PR, et al. A propionyloxy derivative of 11-keto-β-boswellic acid induces apoptosis in HL-60 cells mediated through topoisomerase I & II inhibition. *Chem Biol Interact.* 2011;189(1–2):60–71. Available at: http://doi.org/10.1016/j.cbi.2010.10.017

49. Jamshidi-adegani F, Vakilian S, Al-Hashmi S, et al. Selective anti-cancer activity against melanoma cells using 3-O-acetyl-β-boswellic acid-loaded 3D-Printed scaffold. *Nat Prod Res.* 2023;37(12):2049–2054. Available at: http://doi.org/10.1080/14786419.2022.2116024
50. Pang XF, Yi ZF, Zhang XL, et al. Acetyl-11-keto-β-boswellic acid inhibits prostate tumor growth by suppressing vascular endothelial growth factor receptor 2–mediated angiogenesis. *Cancer Res.* 2009;69(14):5893–5900. Available at: http://doi.org/10.1158/0008-5472.CAN-09-0755
51. Wang C, Wang R, Wang H, et al. A link between chemical structure and biological activity in triterpenoids. *Recent Pat Anticancer Drug Discov.* 2022;17(2):145–161. Available at: http://doi.org/10.2174/1574892816666210512031635
52. Ding Y, Chen MC, Wang M, 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(1):7002. Available at: http://doi.org/10.1038/srep07002
53. Ahmad S, Khan SA, Kindelin A, et al. Acetyl-11-keto-β-boswellic acid (AKBA) attenuates oxidative stress, inflammation, complement activation and cell death in brain endothelial cells following OGD/reperfusion. *Neuromolecular Med.* 2019;21(4):505–516. Available at: http://doi.org/10.1007/s12017-019-08569-z
54. Fathi E, Katouli FH, Riazi GH, et al. The effects of alpha boswellic acid on reelin expression and tau phosphorylation in human astrocytes. *Neuromolecular Med.* 2017;19(1):136–146. Available at: http://doi.org/10.1007/s12017-016-8437-3
55. Wang Y, Xiong ZL, Zhang QY, et al. Acetyl-11-keto-β-boswellic acid accelerates the repair of spinal cord injury in rats by resisting neuronal pyroptosis with Nrf2. *Int J Mol Sci.* 2023;25(1):358. Available at: http://doi.org/10.3390/ijms25010358
56. 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):2867–2884. Available at: http://doi.org/10.1007/s11064-021-03366-2
57. Albekairi TH, Kamra A, Bhardwaj S, et al. Beta-boswellic acid reverses 3-nitropropionic acid-induced molecular, mitochondrial, and histopathological defects in experimental rat model of Huntington's disease. *Biomedicines.* 2022;10(11):2866. Available at: http://doi.org/10.3390/biomedicines10112866
58. Baram SM, Karima S, Shateri S, 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):1101–1112. Available at: http://doi.org/10.1007/s10787-019-00627-z
59. Rajabian A, Sadeghnia HR, Hosseini A, et al. 3-Acetyl-11-keto-β-boswellic acid attenuated oxidative glutamate toxicity in neuron-like cell lines by apoptosis inhibition. *J Cell Biochem.* 2020;121(2):1778–1789. Available at: http://doi.org/10.1002/jcb.29413
60. Marefati N, Beheshti F, Memarpour S, et al. The effects of acetyl-11-keto-β-boswellic acid on brain cytokines and memory impairment induced by lipopolysaccharide in rats. *Cytokine.* 2020;131:155107. Available at: http://doi.org/10.1016/j.cyto.2020.155107
61. Marefati N, Beheshti F, Vafaee F, et al. The effects of incensole acetate on neuro-inflammation, brain-derived neurotrophic factor and memory impairment induced by lipopolysaccharide in rats. *Neurochem Res.* 2021;46(9):2473–2484. Available at: http://doi.org/10.1007/s11064-021-03381-3
62. Raja AF, Ali F, Khan IA, et al. Antistaphylococcal and biofilm inhibitory activities of acetyl-11-keto-β-boswellic acid from Boswellia serrata. *BMC Microbiol.* 2011;11(1):54. Available at: http://doi.org/10.1186/1471-2180-11-54
63. Muralidhar Y, Alpha Raj M, Prasad TNK, et al. Antibacterial, anti-inflammatory and antioxidant effects of acetyl-11-α-keto-β-boswellic acid mediated silver nanoparticles in experimental murine mastitis. *IET Nanobiotechnol.* 2017;11(6):682–689. Available at: http://doi.org/10.1049/iet-nbt.2016.0204
64. Jaroš P, Vrublevskaya M, Lokočová K, et al. Boswellia serrata Extract as an Antibiofilm Agent against Candida spp. *Microorganisms.* 2022;10(1):171. Available at: http://doi.org/10.3390/microorganisms10010171
65. Lei Z, Ren XH, He J, et al. Protective effect of Phaeoporus obliquus polysaccharide against acute liver injury induced by carbon tetrachloride and alcohol in mice. *Pak J Pharm Sci.* 2021;34(2):649–656. Available at: https://pubmed.ncbi.nlm.nih.gov/34275842/
66. Qi XY, Zheng SG, Ma MY, et al. Curcumol suppresses CCF-mediated hepatocyte senescence through blocking LC3B–Lamin B1 interaction in alcoholic fatty liver disease. *Front Pharmacol.* 2022;13:912825. Available at: http://doi.org/10.3389/fphar.2022.912825
67. Chen LC, Hu LH, Yin MC. Alleviative effects from boswellic acid on acetaminophen-induced hepatic injury. *Biomedicine* (*Taipei*). 2016;6(2):9. Available at: http://doi.org/10.7603/s40681-016-0009-1
68. Zaitone SA, Barakat BM, Bilasy SE, et al. Protective effect of boswellic acids versus pioglitazone in a rat model of diet-induced non-alcoholic fatty liver disease: influence on insulin resistance and energy expenditure. *Naunyn Schmiedebergs Arch Pharmacol.* 2015;388(6):587–600. Available at: http://doi.org/10.1007/s00210-015-1102-9
69. Elgazar AA, El-Domany RA, Eldehna WM, et al. 3-Acetyl-11-keto-β-boswellic acid-based hybrids alleviate acetaminophen-induced hepatotoxicity in HepG2 by the regulation of inflammatory and oxidative stress pathways: an integrated approach. *ACS Omega.* 2023;8(42):39490–39510. Available at: http://doi.org/10.1021/acsomega.3c05247
70. Khan A, Khan I, Halim SA, et al. Anti-diabetic potential of β-boswellic acid and 11-keto-β-boswellic acid: Mechanistic insights from computational and biochemical approaches. *Biomed Pharmacother.* 2022;147:112669. Available at: http://doi.org/10.1016/j.biopha.2022.112669
71. Samala S, Veeresham C. Pharmacokinetic and pharmacodynamic interaction of boswellic acids and andrographolide with glyburide in diabetic rats: including its PK/PD modeling. *Phytother Res.* 2016;30(3):496–502. Available at: http://doi.org/10.1002/ptr.5556
72. Pandey RS, Singh BK, Tripathi YB. Extract of gum resins of Boswellia serrata L. inhibits lipopolysaccharide induced nitric oxide production in rat macrophages along with hypolipidemic property. *Indian J Exp Biol.* 2005;43(6):509–516. Available at: https://pubmed.ncbi.nlm.nih.gov/15991575/
73. Liu M, Liu T, Shang P, et al. Acetyl-11-keto-β-boswellic acid ameliorates renal interstitial fibrosis via Klotho/TGF-β/Smad signalling pathway. *J Cell Mol Med.* 2018;22(10):4997–5007. Available at: http://doi.org/10.1111/jcmm.13766
74. Elshazly SM, Abd El Motteleb DM, et al. The selective 5-LOX inhibitor 11-keto-β-boswellic acid protects against myocardial ischemia reperfusion injury in rats: involvement of redox and inflammatory cascades. *Naunyn Schmiedebergs Arch Pharmacol.* 2013;386(9):823–833. Available at: http://doi.org/10.1007/s00210-013-0885-9

75. Gomaa AA, Mohamed HS, Abd-ellatief RB, et al. Advancing combination treatment with glycyrrhizin and boswellic acids for hospitalized patients with moderate COVID-19 infection: a randomized clinical trial. *Inflammopharmacology*. 2022;30(2):477–486. Available at: http://doi.org/10.1007/s10787-022-00939-7
76. Karlapudi V, Sunkara KB, Konda PR, et al. 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. Available at: http://doi.org/10.1080/07315724.2021.2014370
77. Karima S, Aghamollaii V, Mahmoodi Baram S, et al. Boswellic acids improve clinical cognitive scores and reduce systemic inflammation in patients with mild to moderate Alzheimer's disease. *J Alzheimers Dis.* 2023;94(1):359–370. Available at: http://doi.org/10.3233/JAD-221026
78. Valente IVB, Garcia D, Abbott A, et al. The anti-proliferative effects of a frankincense extract in a window of opportunity phase ia clinical trial for patients with breast cancer. *Breast Cancer Res Treat.* 2024;204(3):521–530. Available at: http://doi.org/10.1007/s10549-023-07215-4
79. Badr P, Afsharypuor S, Tohidinik HR, et al. Burn wound healing effect of a sterilized traditional formulation of Boswellia carteri vs. silver sulfadiazine cream 1% in patients presenting second-degree burn wounds: a randomized, double-blind clinical trial. *Iran J Med Sci.* 2023;48(2):137–145. Available at: https://pubmed.ncbi.nlm.nih.gov/36895452/
80. Krüger P, Kanzer J, Hummel J, et al. Permeation of Boswellia extract in the Caco-2 model and possible interactions of its constituents KBA and AKBA with OATP1B3 and MRP2. *Eur J Pharm Sci.* 2009;36(2–3):275–284. Available at: http://doi.org/10.1016/j.ejps.2008.10.005
81. Hüsch J, Bohnet J, Fricker G, et al. Enhanced absorption of boswellic acids by a lecithin delivery form (Phytosome®) of Boswellia extract. *Fitoterapia.* 2013;84:89–98. Available at: http://doi.org/10.1016/j.fitote.2012.10.002
82. Abdel-Tawab M. Considerations to be taken when carrying out medicinal plant research – what we learn from an insight into the IC_{50} values, bioavailability and clinical efficacy of exemplary anti-Inflammatory herbal components. *Pharmaceuticals* (*Basel*). 2021;14(5):437. Available at: http://doi.org/10.3390/ph14050437
83. Bampidis V, Azimonti G, Bastos ML, et al. 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. Available at: http://doi.org/10.2903/j.efsa.2022.7158
84. Krüger P, Daneshfar R, Eckert GP, et al. Metabolism of boswellic acids in vitro and in vivo. *Drug Metab Dispos.* 2008;36(6):1135–1142. Available at: http://doi.org/10.1124/dmd.107.018424
85. Cui YL, Tian XG, Ning J, et al. Metabolic profile of 3-acetyl-11-keto-β-boswellic acid and 11-keto-β-boswellic acid in human preparations in vitro, species differences, and bioactivity variation. *AAPS J.* 2016;18(5):1273–1288. Available at: http://doi.org/10.1208/s12248-016-9945-7
86. Tambe A, Mokashi P, Pandita N. Ex-vivo intestinal absorption study of boswellic acid, cyclodextrin complexes and poloxamer solid dispersions using everted gut sac technique. *J Pharm Biomed Anal.* 2019;167:66–73. Available at: http://doi.org/10.1016/j.jpba.2018.12.018
87. Özsoy M, Atiroğlu V, Guney Eskiler G, et al. A protein-sulfosalicylic acid/boswellic acids @metal–organic framework nanocomposite as anticancer drug delivery system. *Colloids Surf B Biointerfaces.* 2021;204:111788. Available at: http://doi.org/10.1016/j.colsurfb.2021.111788
88. Varia U, Joshi D, Jadeja M, et al. Development and evaluation of ultradeformable vesicles loaded transdermal film of boswellic acid. *Futur J Pharm Sci.* 2022;8:39. Available at: https://www.webofscience.com/wos/woscc/full-record/WOS:000852402000001
89. Badria F, Mazyed E. Formulation of nanospanlastics as a promising approach for improving the topical delivery of a natural leukotriene inhibitor (3-acetyl-11-keto-β-boswellic acid): statistical optimization, in vitro characterization, and ex vivo permeation study. *Drug Design Devel Ther.* 2020;14:3697–3721. Available at: http://doi.org/10.2147/dddt.S265167
90. Goel A, Ahmad FJ, Singh RM, et al. 3-Acetyl-11-keto-β-boswellic acid loaded-polymeric nanomicelles for topical anti-inflammatory and anti-arthritic activity. *J Pharm Pharmacol.* 2010;62(2):273–278. Available at: http://doi.org/10.1211/jpp.62.02.0016
91. Gaur PK, Puri D, Singh AP, et al. Optimization and pharmacokinetic study of boswellic acid–loaded chitosan-guggul gum nanoparticles using box-behnken experimental design. *J Pharm Innov.* 2021;17(2):485–500. Available at: http://doi.org/10.1007/s12247-020-09527-0
92. Bairwa K, Jachak SM. Development and optimisation of 3-Acetyl-11-keto-β-boswellic acid loaded poly-lactic-co-glycolic acid-nanoparticles with enhanced oral bioavailability and in-vivo anti-inflammatory activity in rats. *J Pharm Pharmacol.* 2015;67(9):1188–1197. Available at: http://doi.org/10.1111/jphp.12420
93. Khalaj-Kondori M, Ahmadi-Sani K, Hosseinzadeh A, et al. Dendrosome-encapsulated beta-Boswellic acid boosts expression of the memory-related genes in the B65 cell line. *J Drug Deliv Sci Technol.* 2020;59:101881. Available at: http://doi.org/10.1016/j.jddst.2020.101881
94. Thakur S, Mohan GK. In vivo antiinflammatory activity of facile boswellic acid silver nanoparticles and in vitro drug release kinetics. *BioNanoSci.* 2022;12(2):670–684. Available at: http://doi.org/10.1007/s12668-022-00962-6
95. Ting Y, Jiang Y, Zhao S, et al. Self-nanoemulsifying system (SNES) enhanced oral bioavailability of boswellic acids. *J Funct Foods.* 2018;40:520–526. Available at: http://doi.org/10.1016/j.jff.2017.11.043
96. Majeed M, Natarajan S, Bani S, et al. Mutagenic, genotoxic and sub chronic oral safety analysis of Boswellia Serrata extract (Boswellin® super). *Int J Res Stud Med Health Sci.* 2020;5(7):20–32. Available at: http://doi.org/10.22259/ijrsmhs.0507005
97. Sharma R, Singh S, Singh GD, et al. In vivo genotoxicity evaluation of a plant based antiarthritic and anticancer therapeutic agent Boswelic acids in rodents. *Phytomedicine.* 2009;16(12):1112–1118. Available at: http://doi.org/10.1016/j.phymed.2009.06.009
98. Kiela PR, Midura AJ, Kuscuoglu N, et al. Effects of Boswellia serratain mouse models of chemically induced colitis. *Am J Physiol Gastrointest Liver Physiol.* 2005;288(4):G798–G808. Available at: http://doi.org/10.1152/ajpgi.00433.2004