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

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Author contributions
Na Cui and Mingjie Li conceived the study. Na Cui conducted literature review and wrote the manuscript. Yajun Shi 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.

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Abbreviations
BA, boswellic acids; HPLC, high-performance liquid chromatography; MS, mass spectrometry; α-BA, α-boswellic acid; β-BA, β-boswellic acid; α-BA, α-acetyl-11-keto-boswellic acid; β-BA, β-acetyl-11-keto-boswellic acid; KBA, 11-keto-β-boswellic acid; AKBA, acetyl-11-keto-β-boswellic acid; NSAIDs, nonsteroidal anti-inflammatory drugs; 5-LOX, 5-lipoxygenase; IC50, 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; HD-1, heme oxygenase-1; ROS, reactive oxygen species; MIC, minimum inhibitory concentrations; APAP, acetaminophen; GR, glutathione; COVID-19, coronavirus disease 2019.

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Abstract
Boswellic acids is a general term for a series of pentacyclic triterpenoid compounds that are isolated from the oleogum 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
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 Africa, and its popularity is rising in Western countries. It is the resin of Boswellia carterii Birdw. and Boswellia bhau-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...
acids (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]. Norhiro 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® E1, a standardized extract containing at least 30% AKBA and other β-BA, has been evaluated by Mohammed 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 [36].

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 recombination 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. Butyroxylo and hexanoylo (HKBA) derivatives of KBA demonstrated lower half maximal inhibitory concentration (IC50) values in human promyelocytic leukemia (HL-60) cells compared to the previously reported IC50 of 8.7 μg/mL for the PKBA derivative. The IC50 values for butyroxylo 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 VEGF, 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].
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) [52-97]. 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.

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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 hepatoxic 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/c 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 carmine 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 androgapholide was significantly greater than that of the drug alone and in combination with the control group, suggesting that glibenclamide in combination with BA or androgapholide enhances the hypoglycemic ability of diabetic rats [71]. The hypolipidemic effect of BA has been demonstrated in several studies. The aqueous extract of *Baoswellia serrata* showed strong hypcholesterolemic 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-β1/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 hydroxylated-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® (aprisflex®), 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-b42/amyloid-b40 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 metabolites 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 Casperome™ 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, nanostuctured 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.

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<tr>
<td>Silver nanoparticles</td>
<td>Silver nitrate solution</td>
<td>Carrageenan-induced rat paw edema</td>
<td>Safety, less toxic and therapeutically active</td>
<td>[94]</td>
</tr>
</tbody>
</table>

Table 3 Novel drug delivery systems for BA

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

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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.

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