Boswellia Serrata for Acne Rosacea

by Felician Stancioiu, M.D.

Recurring acne rosacea resistant to Metrogel, successfully treated with Boswellia serrata

Case Report: 65 year old male had acne rosacea - intermittent episodes of maculae and pustules on forehead, cheeks and neck - for more than 15 years; after being diagnosed he was treated with topical metronidazole (Metrogel), initially with some degree of success, but after about 2 years of treatment Metrogel had become ineffective against rosacea.

Another therapeutic intervention was made after a few years with a topical cream containing a cortisol derivative, and for a few weeks of topical steroid application the inflammation and erythema had been under control; however a few weeks after the discontinuation of the cortisol-based treatment the symptoms of rosacea resurfaced. Patient had the following history of disease:

- concurrent symptoms of arthritis – two large joints (shoulder and elbow) painful upon waking up and aggravated with movement and
- GERD (gastro-esophageal reflux disease) with hiatal hernia on EGD (esophagogastroduodenoscopy), concurrent gastritis was treated with proton pump inhibitors for the previous 2 years in 3 week episodes, when symptoms were worsening.
- Hypertension stage 2 was treated with telmisartan in monotherapy for about 1 year
- Type 2 diabetes treated with metformin, dietary changes, also for about 1 year

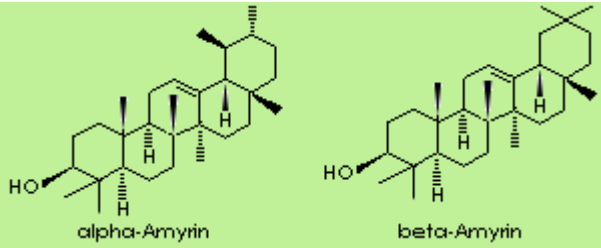
Treatment with Boswellia serrata was initiated for multiple reasons:

Giving long-term anti-inflammatory treatment even with gastric protection would have been a problem considering the concurrent GERD and gastritis, so upon searching anti-inflammatory medications I found out that Boswellia serrata was pretty much the only preparation that did not have such side effects (increasing gastric secretion or gastritis symptoms with long-term administration). Treatment was given with 4 capsules / day, - 2 capsules of 500 mg dry extract of Boswellia serrata each, twice a day (manufacturer Pentavox India) - and alongside with improvement of range of motion and resolution of pain symptoms in the joints affected by arthritis, it was observed that the rosacea was also effectively treated. The duration of the treatment with Boswellia was about 2 months. Furthermore, upon discontinuation of this PO treatment, there was no remission of rosacea for more than 2 years – and continues to this day. Treatment with Boswellia serrata 2 g/day in two divided doses for 4-8 weeks has minimal to none side effects and the effect is as close to a cure as possible.

Even though the underlying pathological mechanism of acne rosacea is not fully understood (besides an increase in inflammation on a predisposing hormonal background), the persistence of the disease-free status after the discontinuation of the treatment and the lack of side effects of this treatment are very strong arguments for which Boswellia serrata should be tried for this dermatologic pathology, especially for difficult-to-treat cases of acnea rosacea.

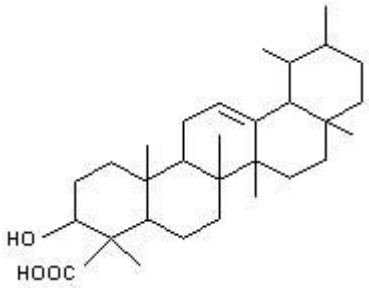
Discussion [1]

The active ingredients of the Boswellia serrata plant extract seem to be boswellic acid and alpha-boswellic acid, although it is probable (as in many plant extracts) that other constituents play an important modulatory role in conveying the full effects observed with the administration of the Boswellia extract. The term boswellic acid itself is applied loosely to a group of compounds with a pentacyclic triterpene structure, which indeed have mainly an anti-inflammatory action. Besides these substances though, the extract also contains monoterpenic substances (alpha-thujene), diterpenes (incensol, incesol-oxyde, iso-incensol-oxyde and a diterpenic alcohol named serratol) and also other triterpenes (alpha- and beta-amyrin). Here we will discuss the triterpenes (boswellic acids and amyrins), for it seems that they are the substances responsible for the effects of the plant extract.

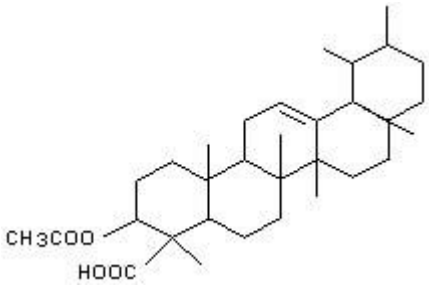


http://chemicalland21.com/lifescience/uh/beta-AMYRIN.htm

Amyrins occur mostly as acetate in latex of rubber trees and they are considered to have broad-spectrum analgesic properties. Alpha-Amyrin is a precursor of Ursolic acid that is obtained by converting the CH_3 in 28 to COOH. Beta Amyrin is a precursor of Boswellic acid that is obtained by converting the CH_3 in 24 to COOH. Ursolic acid has anti elastase activity, and like cholesterol, modulates the membrane fluidity. It prevents UV-B irradiation damages to the skin through prevention of lipid peroxidation and PGE2 release inhibition. Boswellic acid is a strong 5-lipoxigenase inhibitor and it has also anti elastase and anti GAGase properties.



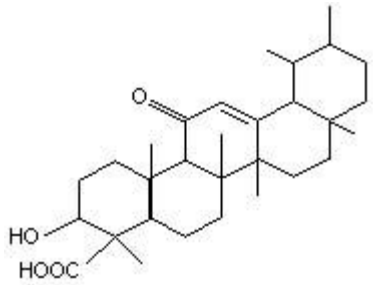
(I) b-boswellic acid



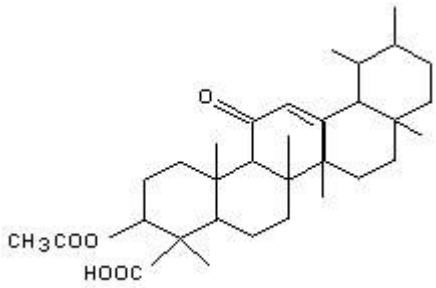
(II) acetyl-b-boswellic acid

[1] Information from the manufacturer's product leaflet, http://www.mskcc.org/mskcc/html/69149.cfm

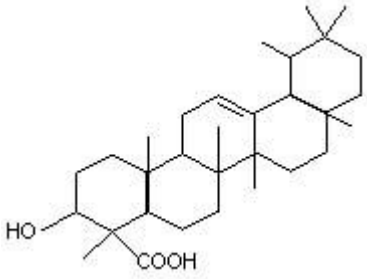
and http://vistapars.com/index.php?option=com_content&view=article&id=1:boswellia-serrata-&catid=1:arthrostopr-rapid&Itemid=155



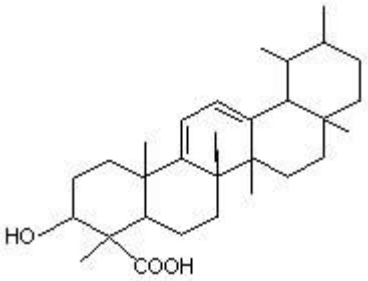
(III) 11-keto-b-boswellic acid (KBA)



(IV) acetyl-11-keto-b-boswellic acid (AKBA)



(V) a-boswellic acid



(VI) g-boswellic acid

From http://www.boswellin.com/mechanism.html

Alpha Amyrin has strong anti-inflammatory activity, is a PKA inhibitor as well as a selective protease inhibitor: chymotrypsin is inhibited at an 18-micromolar level (Rajic: Planta Med 66 206-10 (2000) Hasmeda (Planta med 65 14-8 (1999) confirms this anti protein kinase A (PKA activity) at 8 micromolar. Anti collagenase properties are observed for alpha Amyrin (Kweifio: Res Comm Mol Pathol Pharmacol 85 45-55 (1994). It reduces also the level of 5 lipoxygenase metabolites: 5-HETE and LBT4 as effectively as Indomethacin which confirms the strong anti-inflammatory properties.
DeMiranda: Planta med 66 284-6 (2000) confirms the anti edema properties of alpha Amyrin.
(source: *www.naturactiva.net)*

http://jpet.aspetjournals.org/content/261/3/1143

Mechanism of Action

In vitro studies and animal models show that boswellic acid inhibits 5-lipoxygenase selectively (1) (3) and has anti-inflammatory (13), anti-arthritic, and anti-proliferative effects (2). Boswellia reduces chemically-induced edema and inflammation in rodents. . Boswellic acid was also shown to inhibit NF-KB signaling pathways in macrophages in mouse model of psoriasis, markedly decreasing the production of the pro-inflammatory key cytokine TNF-á and the chemokine MCP-1 (17). This effect was accompanied by the resolution of inflammatory infiltrates and normalization of hyperkeratosis (17).

Unlike other non-steroidal anti-inflammatory drugs, however, boswellic acid has no antipyretic effects and its analgesic action is a consequence of the mitigation of inflammation (16).

Other known actions of boswellia extracts at cellular level are:

- inhibition of the leukocytes infiltration and initial antibody formation (4)

- inhibition of the classic and alternate path of complement activation (7)

- inhibition of the leukocyte 5-lipooxygenase and elastase (4,5,6)

It is important to note that boswellia is one of the very few substances with anti-inflammatory action which does not cause gastric ulcers in animals. This suggests that the action of boswellic acid is through other mechanisms than the inhibition of prostaglandin synthesis, which was confirmed through studies - including (3), which shows that cyclooxygenase path is not inhibited by boswellic acid. Combined with the fact that boswellia, unlike NSAIDs (non-steroidal anti-inflammatory drugs) does not inhibit the synthesis of GAGs (glucose aminoglucans, which are important for the structural integrity of the cartilages in the joints) there is a strong argument for its use in arthritic disease.

So far, based on the known inflammatory effects of this plant and the studies which were performed to show its efficacy and safety, the following pathologies were shown to be mitigated by its administration:

• Arthritis; • Asthma; • Colitis; • Inflammation; • Menstrual cramps

Pharmacokinetics

Two to three hours after an oral dose of 1.2 g dry extract boswellia gum resin, plasma concentrations were measured at 10 to 32 micromolar of 11-keto-beta-boswellic acid and 18 to 20 micromolar of acetyl-11-keto-beta-boswellic acid. (8) Consequently, dosage in the range of 1, 5- 2g/day divided in three daily administrations will maintain a useful plasma concentration for an anti-inflammatory effect in most patients who can benefit from it.

Clinical Summary (from MSKCC website and manufacturer's product leaflet)

Boswellia or Indian frankincense is an ayurvedic herb that is derived from the resin of the plant. It is used traditionally to treat arthritis, ulcerative colitis, coughs, sores, snakebite, and asthma. The major component is boswellic acid [1], which was shown in animal studies to be a potent 5-lipoxygenase inhibitor with anti-inflammatory and antiarthritic effects [1] [2] [3]. Other studies suggest that it has cytotoxic properties [4] [5] [6] [7].
Data from clinical trials indicate effectiveness of Boswellia for bronchial asthma [8]and ulcerative colitis [9]. However, evidence is mixed for its benefits for osteoarthritis [10] [11] and collagenous colitis [12] [13] [14]. Boswellia was also investigated for its role in maintenance of Crohn's disease remission, but it demonstrated no significant benefit [15].
Boswellic acid has fewer adverse effects than steroids and non-steroidal anti-inflammatory drugs. However, its long-term effects on humans are unknown.
Although similar in many functions, boswellia should not be confused with frankincense (Boswellia carteri or B. sacra), guggul or myrrh (Commiphora spp).

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Literature Summary and Critique (MSKCC website)

Gupta I, et al. Effects of gum resin of Boswellia serrata in patients with chronic colitis. *Planta Med* 2001;67:391-5.
Thirty patients with chronic colitis were included in this study. Twenty patients received 300 mg of gum resin of boswellia three times daily for 6 weeks. Ten patients received one gram of sulfasalazine

three times daily for 6 weeks. 90% of the patients treated with boswellia showed an improvement as compared to 60% of the patients treated with sulfasalazine. The author concluded that the gum resin of boswellia could be used to treat chronic colitis with minimal side effects, but larger studies are needed to establish its efficacy and long-term safety.

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   Isomers (alpha- and beta-) of boswellic acids (BAs), 11-keto-beta-BA and their acetyl derivatives were isolated from the gum resin of Boswellia serrata. BA and derivatives concentration dependently decreased the formation of leukotriene B4 from endogenous arachidonic acid in rat peritoneal neutrophils. Among the BAs, acetyl-11-keto-beta-BA induced the most pronounced inhibition of 5-lipoxygenase (5-LO) product formation with an IC50 of 1.5 microM. In contrast to the redox type 5-LO inhibitor nordihydroguaiaretic acid, BA in concentrations up to 400 microM did not impair the cyclooxygenase and 12-lipoxygenase in isolated human platelets and the peroxidation of arachidonic acid by Fe-ascorbate. The data strongly suggest that BAs are specific, nonreducing-type inhibitors of the 5-LO product formation either interacting directly with the 5-LO or blocking its translocation.

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The gum resin of Boswellia serrata, known in Indian Ayurvedic system of medicine as Salai guggal, contains boswellic acids, which have been shown to inhibit leukotriene biosynthesis. In a double-blind, placebo-controlled study forty patients, 23 males and 17 females in the age range of 18 - 75 years having mean duration of illness, bronchial asthma, of 9.58 +/- 6.07 years were treated with a preparation of gum resin of 300 mg thrice daily for a period of 6 weeks. 70% of patients showed improvement of disease as evident by disappearance of physical symptoms and signs such as dyspnoea, rhonchi, number of attacks, increase in FEV subset1, FVC and PEFR as well as decrease in eosinophilic count and ESR. In the control group of 40 patients 16 males and 24 females in the age range of 14-58 years with mean of 32.95 +/- 12.68 were treated with lactose 300 mg thrice daily for 6 weeks. Only 27% of patients in the control group showed improvement. The data show a definite role of gum resin of Boswellia serrata in the treatment of bronchial asthma.

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In this randomized, placebo-controlled, double-blind trial, patients with Crohn's disease (CD) were treated with two oral capsules of 400 mg Boswellia serrata extract (n=42) or placebo (n=40) three times daily for 12 months. Enrolled patients were currently in remission from CD but had experienced at least two documented relapses during the last 4 years. This study found that 59.9% of the Boswellia-treated and 55.3% of the placebo-treated patients maintained remission from Crohn's disease, indicating no statistically significant difference in efficacy between the active and control groups (p=0.085). Time to remission was 171 days for the active group and 185 days for placebo (p=0.69). There was also no statistically significant difference in tolerability between the active and placebo groups (p=0.087). The investigators concluded that Boswellia serrata demonstrated good tolerabilility in the long-term treatment of CD. However, the superiority of this treatment to placebo in the maintenance of CD remission could not be established.

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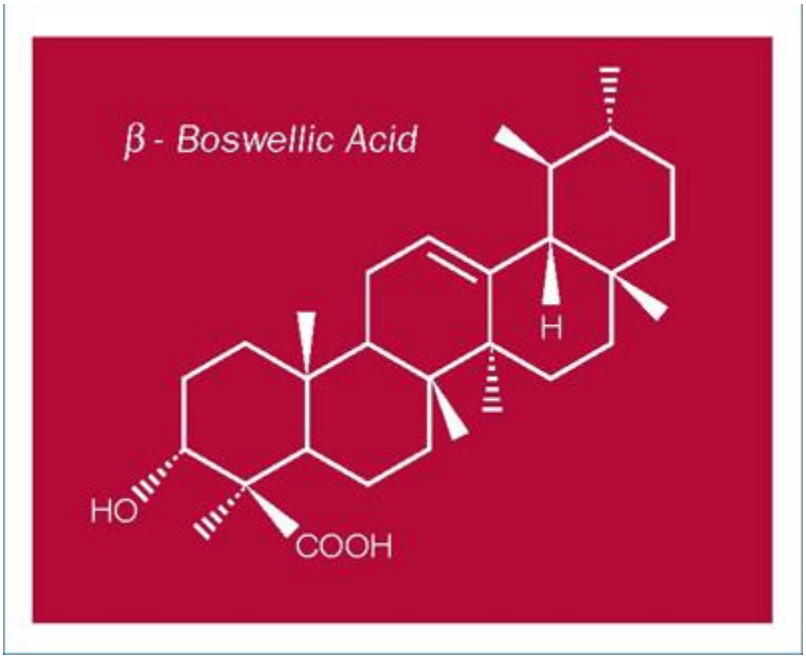
Psoriasis vulgaris is a common chronic inflammatory skin disease involving cytokines and an activated cellular immune system. At variance to skin from patients with atopic dermatitis or from healthy subjects, human psoriatic skin lesions exhibit strong activation of transcription factor NF-kappaB that is mainly confined to dermal macrophages, whereas only a few dendritic cells but no CD3+ lymphocytes show activated NF-kappaB. Since NF-kappaB signaling is required for the induction and/or function of many cytokines and aberrant cytokine expression has been proposed as an underlying cause of psoriasis, we investigated whether NF-kappaB targeting would affect the course of the disease in the CD18 hypomorphic (CD18(hypo)) mouse model of psoriasis. When mice with severe psoriasiform lesions were treated systemically or locally with the IkappaB kinase inhibitor acetyl-11-keto-beta-boswellic acid (AKbetaBA), NF-kappaB signaling and the subsequent NF-kappaB-dependent cytokine production as shown by the TNF-alpha production of macrophages were profoundly suppressed. Additionally, application of the compound counteracted the intradermal MCP-1, IL-12, and IL-23 expression in previously lesional skin areas, led to resolution of the abundant immune cell infiltrates, and significantly reduced the increased proliferation of the keratinocytes. Overall, the AKbetaBA treatment was accompanied by a profound improvement of the psoriasis disease activity score in the CD18(hypo) mice with reconstitution of a nearly normal phenotype within the chosen observation period. Our data demonstrate that NF-kappaB signaling is pivotal for the pathogenesis in the CD18(hypo) mouse model of psoriasis. Therefore, targeting NF-kappaB might provide an effective strategy for the treatment of psoriasis.

Additional information and references on Boswellia is reproduced below and can be found at: http://vistapars.com/index.php?option=com_content&view=article&id=1:boswellia-serrata-&catid=1:arthrostopr-rapid&Itemid=155

Boswellia serrata



Description

Boswellia serrata (frankincense) is a moderate-to-large branching tree (growing to a height of 12 feet) found in India, Northern Africa, and the Middle East. Strips of Boswellia bark are peeled away, yielding a gummy oleo-resin. Extracts of this gummy exudate have been traditionally used in the Ayurvedic system of medicine as an antiarthritic, astringent, stimulant, expectorant, and antiseptic.

Active Constituents

Boswellia contains oils, terpenoids, sugars, and volatile oils. Up to 16 percent of the resin is essential oil, the majority being alpha-thujene and p-cymene. Four pentacyclic triterpene acids are also present, with beta-boswellic acid being the major constituent.

Mechanisms of Action

Animal studies performed in India show ingestion of a defatted alcoholic extract of Boswellia decreased poly-morphonuclear leukocyte infiltration and migration, decreased primary antibody synthesis,[1,2] and almost totally inhibited the classical complement pathway.[3] In an *in vitro* study of the effects of beta-boswellic acid on the complement system, the extract demonstrated a marked inhibitory effect on both the classical and alternate complement pathways.[4] An investigation of Boswellia's analgesic and psychopharmacological effects noted marked sedative and analgesic effects in animal models.[5]

In vitro testing reveals boswellic acids, isolated from the gum resin of Boswellia, in a dose-dependent manner block the synthesis of proinflammatory 5-lipoxygenase products, including 5-hydroxyeicosatetraenoic acid (5-HETE) and leukotriene B4 (LTB4),[6] which cause bronchoconstriction, chemotaxis, and increased vascular permeability.[7] Other anti-inflammatory plant constituents, such as quercetin, also block this enzyme, but they do so in a more general fashion, as an antioxidant; whereas, boswellic acids seem to be specific inhibitors of 5-lipoxygenase.[8,9]

Boswellia inhibits human leukocyte elastase (HLE), which may be involved in the pathogenesis of emphysema. HLE also stimulates mucus secretion and thus may play a role in cystic fibrosis, chronic bronchitis, and acute respiratory distress syndrome.[10,11] Boswellic acids and triterpenoids from *Boswellia serrata* also have an inhibitory and apoptotic effect against the cellular growth of leukemia HL-60 cells.[12-14]

Nonsteroidal anti-inflammatory drugs (NSAIDs) can cause a disruption of glycosaminoglycan synthesis, accelerating articular damage in arthritic conditions.15-18 An in vivo animal study examined Boswellia extract and keto-profen for effects on glycosaminoglycan metabolism. Boswellia significantly reduced the degradation of glycosamino-glycans compared to controls; whereas, ketoprofen caused a decrease in total tissue glycosaminoglycan content.19

Clinical Indications

Inflammatory Bowel Disease

- **Ileitis**

An animal study was conducted to determine the efficacy of Boswellia extract and one of its con-stituents, acetyl-11-keto-β-boswellic acid (AKBA), on leukocyte-endothelial cell interactions in inflammatory bowel disease.20 Ileitis was induced in Sprague-Dawley rats via subcutaneous injection of indomethacin. The animals were then given either Boswellia or AKBA at two different doses (low or high) or placebo. It was observed that Boswellia extract and both potencies of AKBA decreased rolling (up to 90%) and adherent leukocytes (up to 98%), attenuated tissue injury scores, and significantly reduced macroscopic and microscopic inflammation of the gut mucosa.

- **Ulcerative Colitis**

Leukotrienes are believed to play a role in the inflammatory process of ulcerative colitis. Boswellia extract (350 mg three times daily) was compared to sulfasalazine (1 g three times daily) in ulcerative coli-tis patients. Patients on the Boswellia extract showed better improvements than patients on sulfasalazine; 82 percent of Boswellia patients went into remission com-pared with 75 percent on sulfasalazine.[21] A follow-up study of chronic colitis patients taking gum resin of Boswellia (900 mg daily in three divided doses for six weeks) and sulfasalazine (3 g dai-ly in three divided doses for six weeks) again showed similar improvements. Furthermore, 14 of 20 patients (70%) treated with Boswellia serrata gum resin went into remission compared to 4 of 10 patients (40%) treated with sulfasalazine.[22]

- **Crohn's Disease**

Chemical mediators of inflammation were ad-dressed in a clinical trial comparing a Boswellia serrata ex-tract with mesalazine in the treatment of acute Crohn's disease. The protocol population included 44 patients treated with Boswellia extract and 39 patients treated with mesalazine. Between enrollment and end of thera-py, the Crohn's Disease Activity Index decreased signifi-cantly with both Boswellia

extract and mesalazine. Al-though the difference between the two treatments was not statistically significant, the Boswellia extract proved to be as effective as the pharmaceutical.23

Asthma

In a 1998 study of Boswellia's effects on bron-chial asthma, 40 patients took 300 mg of a Boswellia preparation three times daily for six weeks, while an-other 40 patients took a placebo. Seventy percent of pa-tients taking Boswellia demonstrated significant disease improvement, measured by symptomatology and objec-tive measures of lung and immune function; only 27 percent of patients taking a placebo improved.24

Arthritis

In a double-blind, placebo-controlled trial, Bo-swellia demonstrated beneficial effect on knee osteoar-thritis. Thirty patients were given either 1,000 mg Bo-swellia daily or placebo in three divided doses for eight weeks. Patients in the Boswellia group experienced a significant decrease in pain and swelling and increase in range of motion compared to placebo ($p < 0.001$).25

In a double-blind,placebo-controlled,crossover study, Boswellia in combination with ashwagandha, tur-meric, and zinc was studied in osteoarthritis patients.26 Forty-two patients received either the herbal-mineral formulation or placebo for three months, then switched to the other protocol after a 15-day washout period for another three months. The treatment group expe-rienced significant decreases in pain severity ($p<0.001$) and disability scores ($p<0.05$) compared to placebo. Radiological evaluation found no significant changes in either group.

Side Effects and Toxicity

Toxicity studies of Boswellia in rats and pri-mates showed no pathological changes in hematologi-cal, biochemical, or histological parameters at doses up to 1,000 mg/kg. The LD50 has been established at >2 g/kg.28

Dosage

For inflammatory or asthmatic conditions, 300-400 mg of a standardized extract (containing 60% boswellic acids) three times daily is suggested.

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